

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055519 A2

(51) International Patent Classification⁷: **C07D 405/06,**
207/34

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(21) International Application Number: **PCT/IB01/02729**

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(22) International Filing Date:
27 December 2001 (27.12.2001)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(26) Publication Language: English

(30) Priority Data:
60/260,505 9 January 2001 (09.01.2001) US

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PROCESS FOR THE SYNTHESIS OF 5-(4-FLUOROPHENYL)-1-[2-((2R, 4R)-4-HYDROXY-6-OXO-TETRAHYDRO-PYRAN-2-YL)-ETHYL]-2-ISOPROPYL-4-PHENYL-1H-PYRROLE-3-CARBOXYLIC ACID PHENYLAMIDE

(57) Abstract: An improved process for the preparation of 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide by a novel synthesis is described where methyl cyanoacetate is converted in eight operations or fewer to the desired product, as well as other valuable intermediates used in the process.

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NOVEL PROCESS FOR THE SYNTHESIS OF 5-(4-FLUOROPHENYL)-1-
[2-((2R,4R)-4-HYDROXY-6-OXO-TETRAHYDRO-PYRAN-2-YL)-ETHYL]-
2-ISOPROPYL-4-PHENYL-1H-PYRROLE-3-CARBOXYLIC ACID
PHENYLAMIDE

5

FIELD OF THE INVENTION

An improved synthesis for the preparation of 5-(4-fluorophenyl)-1-
[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-
1H-pyrrole-3-carboxylic acid phenylamide is described where methyl
cyanoacetate is converted in eight operations or fewer to the desired product, as
well as other valuable intermediates used in the process.

10

BACKGROUND OF THE INVENTION

5-(4-Fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-
2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide is a
valuable intermediate in the synthesis of Lipitor® (atorvastatin calcium) known
by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-
methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid
calcium salt (2:1) trihydrate. The aforementioned compound is useful as an
inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase
(HMG-CoA reductase) and is thus useful as a hypolipidemic and/or
hypocholesterolemic agent.

15

20

United States Patent No. 4,681,893, which is herein incorporated by
reference, discloses certain *trans*-6-[2-(3- or 4-carboxamido-substituted-pyrrol-
1-yl)alkyl]-4-hydroxy-pyran-2-ones including *trans* (±)-5-(4-fluorophenyl)-
2-(1-methylethyl)-N, 4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-
2-yl)ethyl]-1H-pyrrole-3-carboxamide.

25

United States Patent No. 5,273,995, which is herein incorporated by
reference, discloses the enantiomer having the (R,R) form of the ring-opened acid
of *trans*-5-(4-fluorophenyl)-2-(1-methylethyl)-N, 4-diphenyl-1-[(2-tetrahydro-4-

-2-

hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e.,
[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

United States Patent Nos. 5,003,080; 5,097,045; 5,103,024; 5,124,482;
5 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792;
5,342,952; 5,298,627; 5,446,054; 5,470,981; 5,489,690; 5,489,691; 5,510,488;
5,998,633; and 6,087,511, which are herein incorporated by reference, disclose
various processes and key intermediates for preparing atorvastatin.

Crystalline forms of atorvastatin calcium are disclosed in United States
10 Patent Nos. 5,969,156 and 6,121,461 which are herein incorporated by reference.

A synthetic procedure for the preparation of 5-(4-fluorophenyl)-1-[2-
((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-
1H-pyrrole-3-carboxylic acid phenylamide is disclosed in United States Patent
No. 5,273,995.

15 The asymmetric reduction of β -ketoesters, as well as β -diketones, is a
well-established transformation in organic synthesis. However, the complexity of
these reactions increases in the case of 1,3,5-tricarbonyl systems and poor yields
and poor stereoselectivities often result. In fact, investigations by Saburi
(*Tetrahedron*, 1997, 1993;49) and Carpentier (*Eur. J. Org. Chem.* 1999;3421)
20 have independently demonstrated low to moderate diastereo- and/or enantio-
selectivities for diketoester asymmetric hydrogenations. Furthermore, the fact that
the processes in the prior art require high pressure hydrogenation and extended
reaction times makes these procedures impractical and not amenable to large-scale
manufacturing processes.

25 However, we have surprisingly and unexpectedly found that the diol esters
of the present invention, (R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-
phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid esters, can be
obtained directly from the corresponding 1,3,5-tricarbonyl precursors in a highly
stereoselective manner via a mild and efficient ruthenium-catalyzed asymmetric
30 hydrogenation reaction utilizing chiral non-racemic diphosphine ligands in the
presence of secondary activating agents such as protic acids.

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The object of the present invention is a short and efficient process for the preparation of 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide. The present process avoids the use of a costly chiral raw material

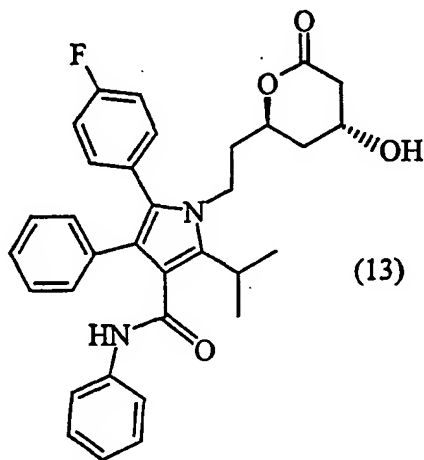
5 ((R)-4-cyano-3-hydroxy-butyric acid ethyl ester), and a low temperature diastereoselective borane reduction. Furthermore, a key Paal-Knorr condensation step, common to the present and prior art processes, has been improved through a significant decrease in reaction time.

Thus, the present process has significant advantages over the prior art

10 processes and is amenable to large-scale synthesis.

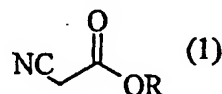
SUMMARY OF THE INVENTION

Accordingly, the first aspect of the present invention is an improved process for the preparation of a compound of Formula (13)

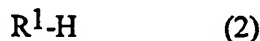


15 which comprises:

Step (a) reacting a compound of Formula (1)



wherein R is alkyl, aryl, arylalkyl, or heteroaryl in a solvent with a compound of Formula (2)



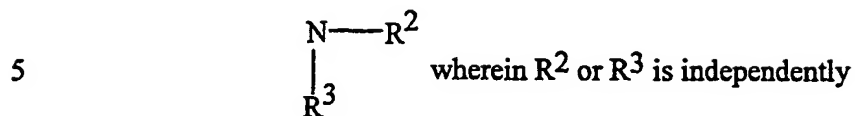
-4-

wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is



alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

10 R^2 and R^3 together are

-(CH₂)₄-,

-(CH₂)₅-,

-(CH(R⁴)-CH₂)₃-,

-(CH(R⁴)-CH₂)₄-,

15 -(CH(R⁴)-(CH₂)₂-CH(R⁴))-,

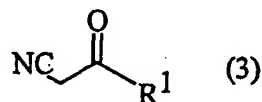
-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,

-CH₂-CH₂-A-CH₂-CH₂-,

-CH(R⁴)-CH₂-A-CH₂CH₂-,

-CH(R⁴)-CH₂-A-CH₂-CH(R⁴)-

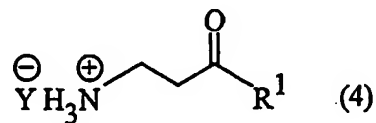
20 wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or
N and R is as defined above to afford a compound of
Formula (3)



wherein R^1 is as defined above;

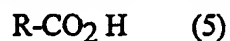
-5-

Step (b) reacting a compound of Formula (3) with hydrogen in the presence of a catalyst and a strong acid in a solvent to afford a compound of Formula (4)

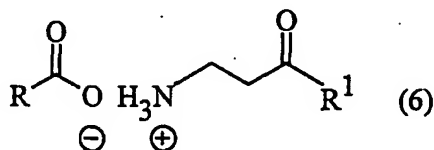


5 wherein Y is Cl, Br, TsO, MsO, or HSO₄, and R¹ is as defined above;

Step (c) reacting a compound of Formula (4) with a base in a solvent followed by the addition of a compound of Formula (5)

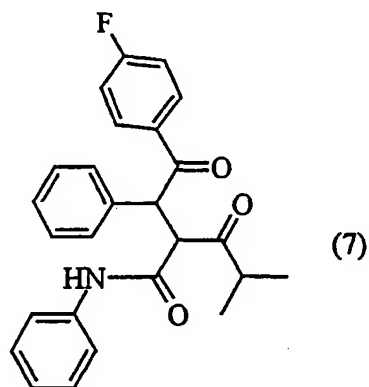


wherein R is as defined above in a solvent to afford a compound of Formula (6)



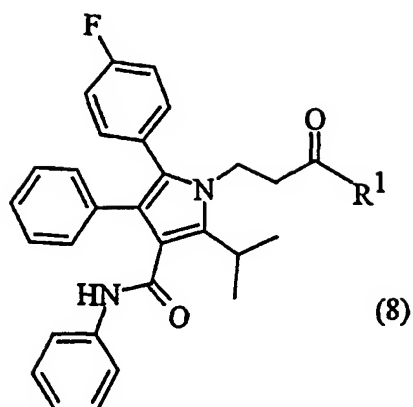
wherein R and R¹ are as defined above;

Step (d) reacting a compound of Formula (6) with Compound (7)



15 in a solvent with removal of water to afford a compound of Formula (8)

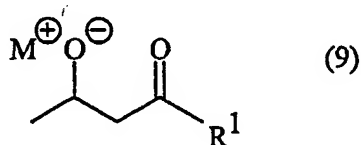
-6-



(8)

wherein R^1 is as defined above;

Step (e) reacting a compound of Formula (8) with a compound of Formula (9)

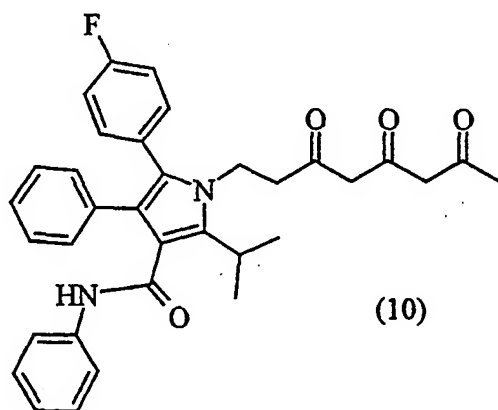


(9)

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wherein M is sodium, lithium, potassium, zinc, magnesium, copper,

calcium, or aluminum and R¹ is as defined above, in a solvent in the presence of a strong base to afford a compound of Formula (10)



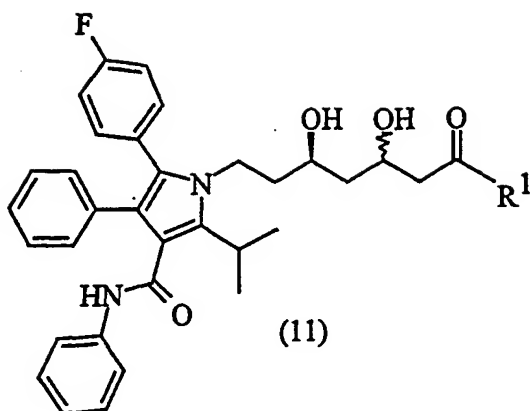
(10)

10

wherein R^1 is as defined above;

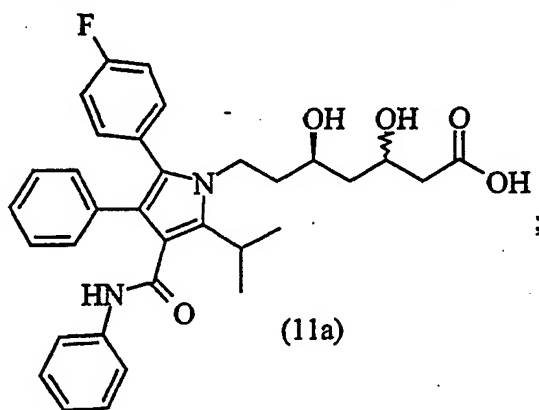
Step (f) reacting a compound of Formula (10) with hydrogen in the presence of a catalyst in a solvent in the presence of an acid to afford a compound of Formula (11)

-7-



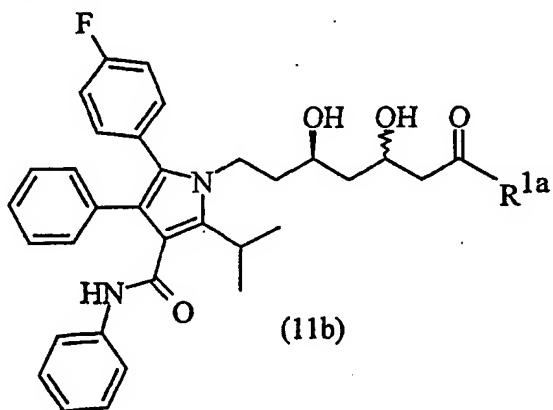
(11)

wherein R¹ is as defined above or a compound of Formula (11a)



(11a)

Step (g) reacting a compound of Formula (11b)



(11b)

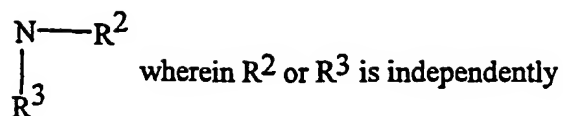
wherein R^{1a} is OH, -XR wherein

X is O,

S, or

Se, or R^{1a} is

-8-



alkyl,
cycloalkyl,
arylalkyl, or
aryl, or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

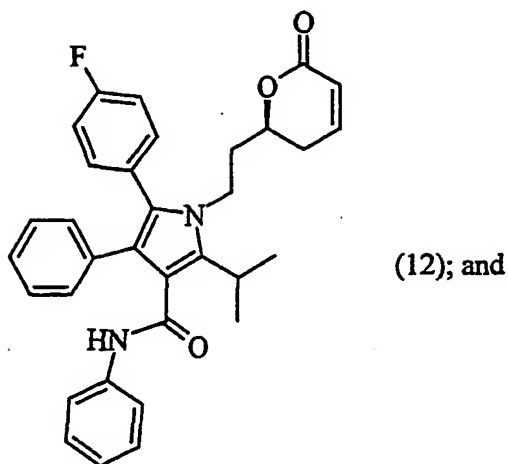
$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and R is as defined above in a solvent in the presence of an acid, followed by reaction with a base, an acylating agent, and an acylation catalyst in a solvent to afford a compound of Formula (12)

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(12); and

Step (h) reacting a compound of Formula (12) with HO-M in an alcohol of Formula (17) or (17b)

HOCH₂-Aryl (17) or HO-Allyl (17b)

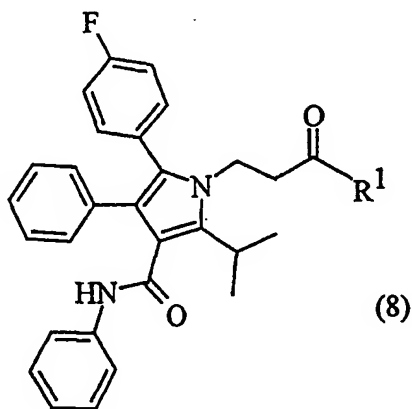
5 wherein M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum; or with a compound of Formula (16) or (16b)

$M^{\oplus} OCH_2\text{-Aryl (16) or } M^{\oplus} O\text{-Allyl (16b)}$

wherein M is as defined above in an alcohol of Formula (17) or (17b)

10 wherein aryl or allyl in a compound of Formula (16) or (16b) and (17) or (17b) is the same, in a solvent followed by the addition of hydrogen in the presence of a catalyst and an acid to afford the compound of Formula (13).

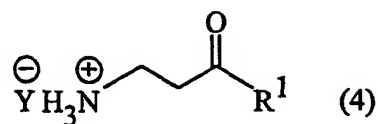
A second aspect of the present invention is an improved process for the preparation of a compound of Formula (8).



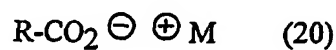
(8)

15 wherein R¹ is as defined above which comprises:
reacting a compound of Formula (4)

-10-

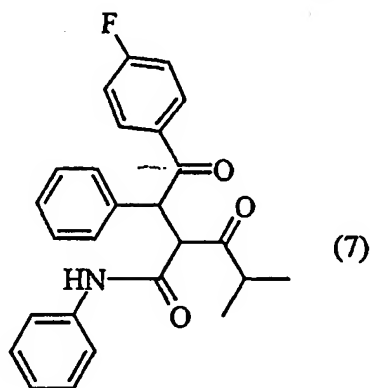


wherein Y is Cl, Br, TsO, MsO, or HSO₄, and R¹ is as defined above with a compound of Formula (20)



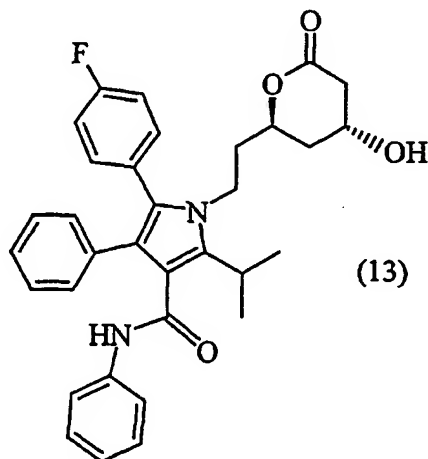
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wherein R and M are as defined above with Compound (7)



in a solvent with removal of water to afford a compound of Formula (8).

A third aspect of the present invention is an improved process for the preparation of compound (13)



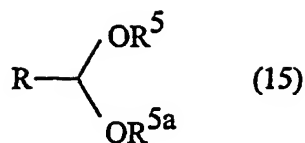
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which comprises:

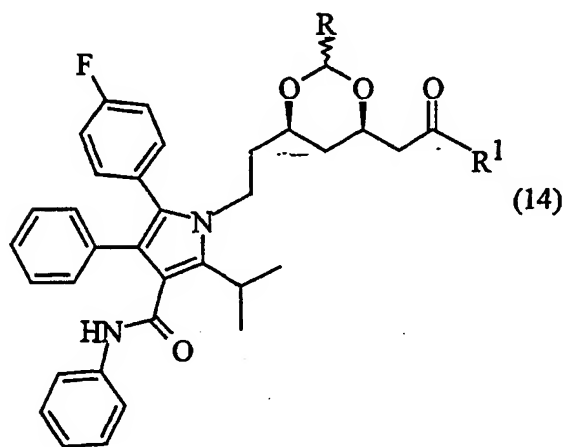
Step (a) reacting a compound of Formula (11) with an acetal of Formula

(15)

-11-



wherein R^5 and R^{5a} are independently the same or different and are,
methyl, ethyl, or $-(\text{CH}_2)_n-$ wherein n is an integer of 2 to 4, and R
is as defined above in a solvent in the presence of an acid followed
by the addition of an aldehyde corresponding to the previous acetal
in the presence of a base to afford a compound of Formula (14)



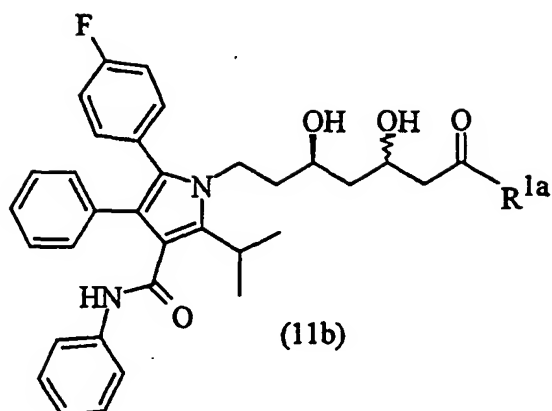
wherein R^1 and R are as defined above;

Step (b) reacting a compound of Formula (14) in a nucleophilic solvent in
the presence of an acid or optionally reaction with hydrogen in the presence of a
catalyst and an acid in a solvent to afford the compound of Formula (13); and

Step (c) alternatively, reacting a compound of Formula (11) or (11a) in a
non-nucleophilic solvent in the presence of an acid to afford a compound of
Formula (13).

A fourth aspect of the present invention is a process for the preparation of
a compound of Formula (11b)

-12-

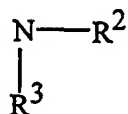


wherein R^{1a} is OH, -XR wherein

X is O,

S, or

Se, or R^{1a} is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

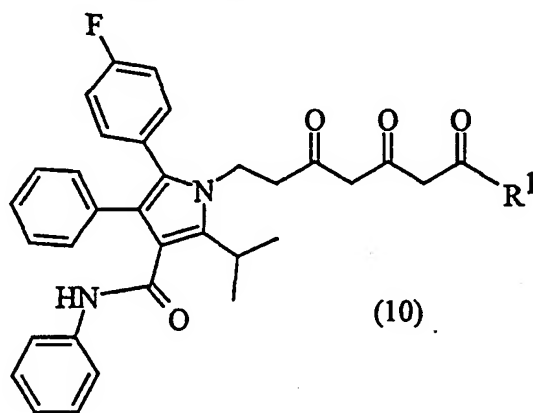
$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

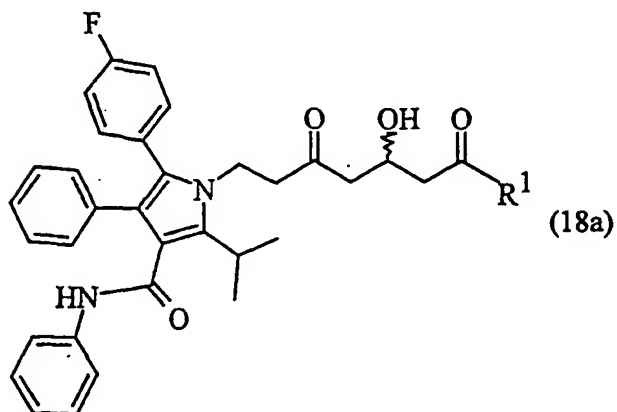
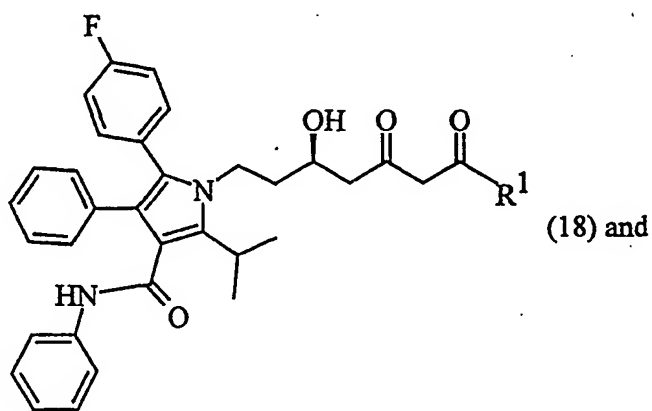
$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

wherein R⁴ is alkyl of from one to four carbon atoms, A is O, S, or N, and R is alkyl, aryl, arylalkyl, or heteroaryl which comprises:

Step (a) reacting a compound of Formula (10)



5 wherein R¹ is as defined above with one mole of hydrogen in the presence
of a catalyst in a solvent in the presence of an acid to afford compounds of
Formula (18) and/or Formula (18a)

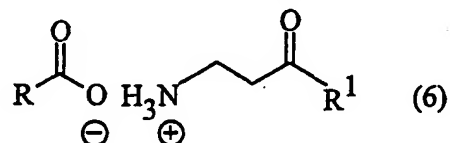


-14-

wherein R^1 is as defined above; and

Step (b) reacting either a compound of Formula (18) or (18a) with hydrogen in the presence of a catalyst in a solvent in the presence of an acid to afford a compound of Formula (11b).

5 A fifth aspect of the present invention is a compound of Formula (6)

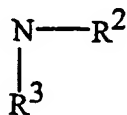


wherein R is alkyl, aryl, arylalkyl, or heteroaryl, and R^1 is XR wherein

X is O,

10 S, or

Se, or R^1 is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

15 arylalkyl, or

aryl or

R^2 and R^3 together are

-(CH₂)₄-,

-(CH₂)₅-,

20 -(CH(R⁴)-CH₂)₃-,

-(CH(R⁴)-CH₂)₄-,

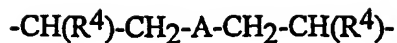
-(CH(R⁴)-(CH₂)₂-CH(R⁴))-,

-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,

-CH₂-CH₂-A-CH₂-CH₂-,

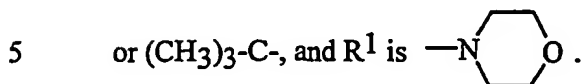
25 -CH(R⁴)-CH₂-A-CH₂CH₂-,

-15-

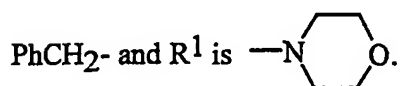


wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N and R is as defined above.

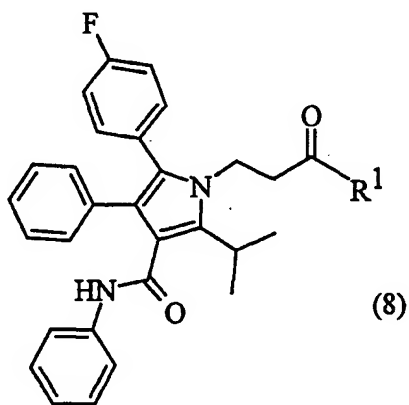
Particularly preferred, is a compound of Formula (6) wherein R is PhCH_2-



More particularly preferred, is a compound of Formula (6) wherein R is



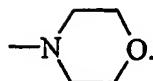
A sixth aspect of the present invention is a compound of Formula (8)



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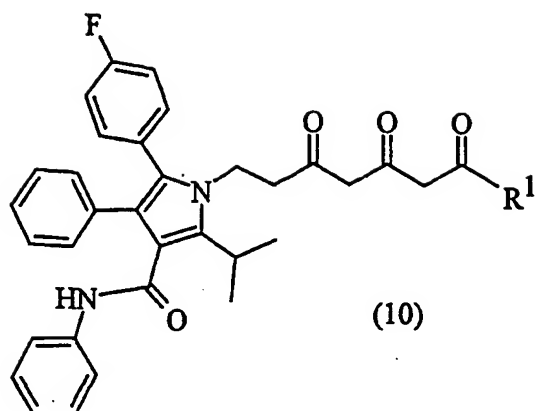
wherein R^1 is as defined above.

Particularly preferred is a compound of Formula (8) wherein R^1 is



A seventh aspect of the present invention is a compound of Formula (10) or a pharmaceutically acceptable salt thereof

-16-



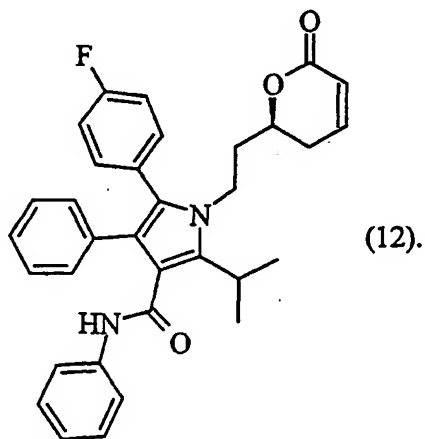
wherein R^1 is as defined above.

Particularly preferred is a compound of Formula (10) wherein R^1 is

-O-tertiary butyl, -O-isopropyl, -O-ethyl, -O-methyl, ---N---O , or -NMe₂.

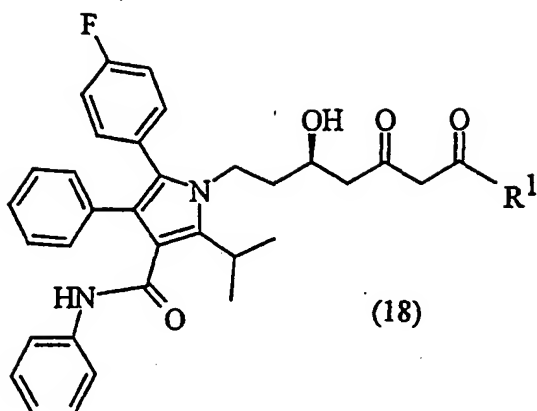
5

An eighth aspect of the present invention is the compound of Formula (12)



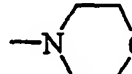
A ninth aspect of the present invention is a compound of Formula (18) or a pharmaceutically acceptable salt thereof

-17-



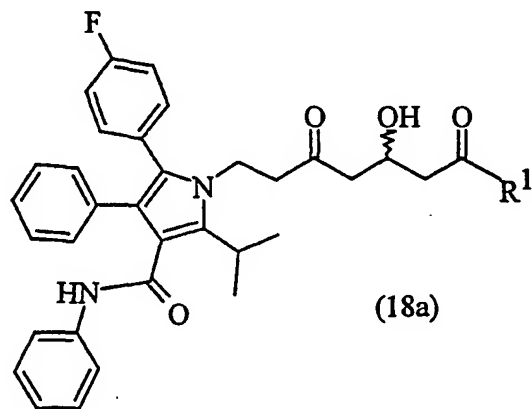
wherein R¹ is as defined above.

Particularly preferred is a compound of Formula (18) wherein R¹ is

-O-tertiary butyl, -O-isopropyl, -O-ethyl, -O-methyl, , or -NMe₂.

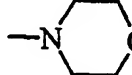
5

A tenth aspect of the present invention is a compound of Formula (18a) or a pharmaceutically acceptable salt thereof



wherein R¹ is as defined above.

Particularly preferred is a compound of Formula (18a) wherein R¹ is

10 -O-tertiary butyl, -O-isopropyl, -O-ethyl, -O-methyl, , or -NMe₂.

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DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 8 carbon atoms and includes, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec-butyl, isobutyl, *tert*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like.

"Alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "alkyl".

The term "cycloalkyl" means a saturated hydrocarbon ring having 3 to 8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "aryl" means an aromatic radical which is a phenyl group, a phenylalkyl group, a phenyl group substituted by 1 to 4 substituents selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, halogen, trifluoromethyl, dialkylamino as defined above for alkyl, nitro, cyano,

O
||
-C-N(alkyl)₂ as defined above for alkyl, -(CH₂)_n-N(alkyl)₂ wherein n² is an integer of 1 to 5 and alkyl is defined above

O
||
and -(CH₂)_n-N-C-alkyl as defined above for alkyl and n².
|
alkyl

The term "allyl" means a hydrocarbon radical of 3 to 8 carbon atoms, containing a double bond between carbons 2 and 3, unsubstituted or substituted by 1 to 3 substituents on the carbons containing the double bond selected from alkyl or aryl as defined above, and includes, for example, propenyl, 2-butenyl, cinnamyl, and the like.

The term "arylalkyl" means an aromatic radical attached to an alkyl radical wherein aryl and alkyl are as defined above for example, benzyl, phenylethyl, 3-phenylpropyl, (4-chlorophenyl)methyl, and the like.

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

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"Alkaline-earth metal" is a metal in Group IIA of the periodic table and includes, for example, calcium, barium, strontium, magnesium, and the like.

The term "heteroaryl" means a 5- and 6-membered heteroaromatic radical which may optionally be fused to a benzene ring containing 1 to 3 heteroatoms selected from N, O, and S and includes, for example, a heteroaromatic radical which is 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 3-, or 4-pyridinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-5-yl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5-pyrazolyl, or 2- or 5-thiadiazolyl and the like optionally substituted by a substituent selected from alkyl as defined above, alkoxy as defined above, thioalkoxy as defined above, halogen, trifluoromethyl, dialkylamino as defined above for alkyl, nitro, cyano,

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{N}(\text{alkyl})_2 \end{array}$ as defined above for alkyl, $-(\text{CH}_2)_{n^2}-\text{N}(\text{alkyl})_2$ wherein n^2 is an

integer of 1 to 5, and alkyl is as defined above, and $-(\text{CH}_2)_{n^2}-\text{N}-\text{C} \begin{array}{c} \text{O} \\ \parallel \\ | \\ \text{alkyl} \end{array}$ as

defined above for alkyl and n^2 .

Pharmaceutically acceptable acid addition salts of the compounds of the present invention include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like.

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Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma. Sci.*, 1977;66:1).

5 The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are
10 equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chlorprocaine,
15 choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977;66:1).

20 The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of
25 the present invention.

Additionally, the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

30 The following list contains abbreviations and acronyms used within the schemes and text:

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	H ₂ SO ₄	Sulfuric acid
	NaOMe	Sodium methoxide
	MeOH	Methanol
	MtBE	Methyl tert-butyl ether
5	GC	Gas chromatography
	Pt/C	Platinum on carbon
	Pd/C	Palladium on carbon
	H ₂	Hydrogen
	HCl	Hydrochloric acid
10	Hg	Mercury
	psi	Pounds per square inch
	iPrOH (IPA)	Isopropyl alcohol
	HPLC	High pressure liquid chromatography
	NaOH	Sodium hydroxide
15	CH ₂ Cl ₂	Dichloromethane (methylene chloride)
	DMSO-d ₆	Deuterated dimethylsulfoxide
	THF	Tetrahydrofuran
	Na ₂ SO ₄	Sodium sulfate
	nBuLi	n-Butyllithium
20	NaCl	Sodium chloride
	KOtBu	Potassium tert-butoxide
	NaHCO ₃	Sodium bicarbonate
	BnOH	Benzyl alcohol
	Pd(OH) ₂ /C	Palladium hydroxide on carbon
25	H ₂ O	Water
	PivOH	Pivalic acid
	PhCHO	Benzaldehyde
	PhCH ₃	Toluene
	CDCl ₃	Deuterated chloroform
30	BnONa	Sodium benzylate
	NH ₄ OH	Ammonium hydroxide

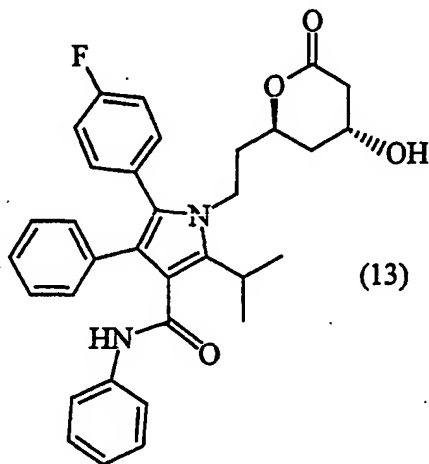
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	PhCH(OMe) ₂	Benzaldehyde dimethyl acetal
	MsOH	Methanesulfonic acid
	pTsOH	para Toluenesulfonic acid
	CSA	Camphorsulfonic acid
5	Ph	Phenyl
	NaH	Sodium hydride
	KH	Potassium hydride
	EtOAc	Ethyl acetate
	tBuOH(HOtBu)	tert-Butanol
10	PhCH ₂ CO ₂ H	Phenylacetic acid
	NaNH ₂	Sodium amide
	KHMDS	Potassium hexamethyldisilazide
	LAH	Lithium aluminum hydride
	Pd/Al ₂ O ₃	Palladium on alumina
15	APCI	Atmospheric pressure chemical ionization
	ESI	Electrospray ionization
	DCI	Direct chemical ionization
	¹ H NMR	Proton nuclear magnetic resonance spectroscopy
	¹³ C NMR	¹³ Carbon nuclear magnetic resonance spectroscopy
20	BINAP	(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
	pTol-BINAP	(R)-(+)-Bis(di-p-tolyl-phosphino)-1,1'-binaphthyl
	Cl-MeO-BIPHEP	[(R)-(+)-5,5'-Dichloro-6,6'-dimethoxy[1,1'-biphenyl]-2,2'-diyl]-bis-diphenylphosphine
25	C2-TunaPhos	[(12aR)-6,7-dihydrodibenzo[e,g][1,4]dioxocin-1,12-diyl]-bis-diphenylphosphine
	C4-TunaPhos	[(14aR)-6,7,8,9-tetrahydrodibenzo[b,d][1,6]dioxecin-1,14-diyl]-bis-diphenylphosphine
	MeO-BIPHEP	[(1S)-(-)-6,6'-Dimethoxy[1,1'-biphenyl]-2,2'-diyl]-bis-diphenylphosphine
30	p-cymene	4-isopropyltoluene
	ee	Enantiomeric excess

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HRMS	High resolution mass spectrometry
m/z	Mass to charge ratio
t_R	Retention time

5 The process of the present invention in its first aspect is a new, improved, economical, and commercially feasible method for the preparation of the compound of Formula (13)

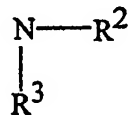


The process of the present invention in its first aspect is outlined in Scheme 1. Thus, a compound of Formula (1) wherein R is alkyl, aryl, arylalkyl, or
 10 heteroaryl is reacted with a compound of Formula (2) wherein R^1 is -XR wherein

X is O,

S,

Se or R^1 is



wherein R^2 or R^3 is independently

15

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

R^2 and R^3 together are

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-(CH₂)₄-,-(CH₂)₅-,-(CH(R⁴)-CH₂)₃-,-(CH(R⁴)-CH₂)₄-,5 -(CH(R⁴)-(CH₂)₂-CH(R⁴))-,-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,-CH₂-CH₂-A-CH₂-CH₂-,-CH(R⁴)-CH₂-A-CH₂CH₂-,-CH(R⁴)-CH₂-A-CH₂-CH(R⁴)-

10 wherein R⁴ is alkyl of from one to four carbon atoms, A is O, S, or N and
 R is as defined above in a solvent such as, for example, methyl
 tertiary butyl ether, and the like, to afford a compound of
 Formula (3) whereas R¹ is as defined above. Preferably, the
 reaction is carried out with a compound of Formula (2) wherein
 15 R¹-H is morpholine in methyl tertiary butyl ether.

 A compound of Formula (3) is reacted with hydrogen in the presence of a
 catalyst such as, for example, Pt/C, Pd/C in the presence of an acid such as, for
 example, a strong acid, for example, hydrochloric acid, hydrobromic acid,
 p-toluenesulfonic acid, methanesulfonic acid, sulfuric acid, and the like
 20 (optionally the reduction is carried out with Sponge Ni/NH₄OH, metal hydrides,
 and the like, to afford the free base of a compound of Formula (4)) in a solvent
 such as, for example, methanol, ethanol, and the like to afford a compound of
 Formula (4) wherein Y is Cl, Br, TsO, MsO, or HSO₄ and R¹ is as defined above.

 Preferably, the reaction is carried out in the presence of Pt/C, hydrochloric
 25 acid and hydrogen in methanol.

 A compound of Formula (4) is reacted with a base such as, for example,
 sodium methoxide and the like in a solvent such as, for example, tetrahydrofuran,
 toluene, methyl tertiary butyl ether, and the like, and in an alcohol such as, for
 example, isopropanol, ethanol, methanol, and the like, to afford the free base

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followed by reaction with a compound of Formula (5) wherein R is as defined above in a solvent such as, for example, isopropanol, tetrahydrofuran, and the like to afford a compound of Formula (6) wherein R is as defined above. Optionally, the free base of a compound of Formula (4) may be reacted with a compound of Formula (5) to afford a compound of Formula (6). Preferably, the reaction is carried out with sodium methoxide in methyl tertiary butyl ether and methanol to afford the free base followed by reaction with phenylacetic in tetrahydrofuran.

A compound of Formula (6) is reacted with the compound of Formula (7) in a solvent such as, for example, a protic, an aprotic, a polar or a non-polar solvent, for example, tetrahydrofuran and the like with removal of water with the aid of a chemical drying agent such as, for example, molecular sieves and the like or with the aid of a Dean-Stark water trap or using azeotropic distillation with a suitable solvent such as, for example toluene and the like to afford a compound of Formula (8) wherein R¹ is as defined above. Preferably, the reaction is carried out with activated 3A molecular sieves in tetrahydrofuran.

A compound of Formula (8) is reacted with a compound of Formula (9) wherein M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum and R¹ is as defined above in a solvent such as, for example, a nonreactive aprotic solvent, for example, tetrahydrofuran, toluene, and the like in the presence of a strong base such as, for example, *n*-butyllithium, lithium or potassium hexamethyldisilazide, lithium diisopropylamide, and the like to afford a compound of Formula (10) wherein R¹ is as defined above. Preferably, the reaction is carried out with a compound of Formula (9) wherein M is sodium, the base is *n*-butyllithium and the solvent is tetrahydrofuran.

The carbonyls of a compound of Formula (10) in Scheme 1 are shown in the keto form. However, a compound of Formula (10) can undergo "keto-enol" tautomerism and thus can exist in several tautomeric forms which are encompassed within the present invention.

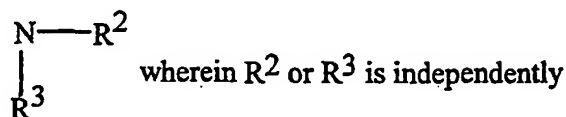
A compound of Formula (10) is treated with hydrogen in the presence of a catalyst such as, for example, a chiral non-racemic ruthenium (II)-diphosphine complex. For example, a ruthenium catalyst precursor such as [dichloro-(1,5-cyclooctadiene)] ruthenium (II) oligomer and chiral diphosphine ligand such as

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[(R)-(+)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphthyl]. However, any chiral non-racemic ruthenium (II)/diphosphine combination may be employed in this reduction reaction. For example, ruthenium (II) catalyst precursors include [dibromo-(1,5-cyclooctadiene)] ruthenium (II) dimer, [bis-(2-methallyl)cycloocta-1,5-diene] ruthenium (II) complex and [dichloro(*p*-cymene)] ruthenium (II) dimer, and the like. Examples of effective chiral diphosphine ligands include 2,2'-bis(di-*p*-tolyl-phosphino)-1,1'-binaphthyl, 2-diphenyl-phosphinomethyl-4-diphenylphosphino-1-*tert*-butoxy-carbonylpyrrolidine, tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,11-diyl-bis(diphenylphosphine) derivatives, 4,4'-bidibenzofuran-3,3'-diylbis(diphenylphosphine), 6,6'-dimethoxy[1,1'-biphenyl]-2,2'-diyl]bis-diphenylphosphine, [5,5'-dichloro-6,6'-dimethoxy[1,1'-biphenyl]-2,2'-diyl]-bis-diphenylphosphine, and 1,2-bis(2,5-dimethylphospholano) derivatives and the like in a solvent such as, for example, methanol, ethanol, isopropanol, and the like, optionally in the presence of a co-solvent, for example, dichloromethane, tetrahydrofuran, toluene and the like in the presence of an acid such as, for example, hydrochloric acid, hydrobromic acid, Dowex® ion exchange resin, and the like to afford a compound of Formula (11) or a compound of Formula (11a) wherein R¹ is as defined above. Preferably, the reaction is carried out with dichloro(*p*-cymene) ruthenium (II) dimer and [(R)-(+)-5,5'-dichloro-6,6'-dimethoxy[1,1'-biphenyl]-2,2'-diyl]-bis-diphenylphosphine in methanol in the presence of hydrobromic acid.

A compound of Formula (11b) wherein R^{1a} is wherein R^{1a} is OH, -XR wherein

25 X is O,
S, or
Se, or R^{1a} is



alkyl,
30 cycloalkyl,

-27-

arylalkyl, or

aryl, or

 R^2 and R^3 together are-(CH₂)₄-,-(CH₂)₅-,-(CH(R⁴)-CH₂)₃-,-(CH(R⁴)-CH₂)₄-,-(CH(R⁴)-(CH₂)₂-CH(R⁴))-,-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,-CH₂-CH₂-A-CH₂-CH₂-,-CH(R⁴)-CH₂-A-CH₂CH₂-,-CH(R⁴)-CH₂-A-CH₂-CH(R⁴)-

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and R is alkyl, aryl, arylalkyl, or heteroaryl is reacted with an acid such as, for example, *p*-toluenesulfonic acid, camphor-sulfonic acid, sulfuric acid, hydrogen chloride, and the like in a non-nucleophilic solvent such as, for example, toluene, acetonitrile, dichloromethane, methyl tertiary butyl ether, and the like, followed by reaction with a base, such as, for example, triethylamine, pyridine, diisopropylethylamine, and the like, and with an acylating agent, such as, for example, acetic anhydride, benzoyl chloride, benzyl chloroformate, and the like, in the presence of 4-dimethylaminopyridine to afford the compound of Formula (12). Preferably, the reaction is carried out in toluene in the presence of *p*-toluenesulfonic acid, followed by treatment with triethylamine, acetic anhydride, and 4-dimethylaminopyridine in toluene.

A compound of Formula (12) is reacted with HO-M in an alcohol of Formula (17) or (17b) wherein M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum, or with a compound of Formula (16) or (16b) wherein M is as defined above in an alcohol of Formula (17) or (17b) wherein aryl or allyl in a compound of Formula (16) or (16b) and (17) or (17b) is the same, in an optional cosolvent, such as, for example, a nonnucleophilic solvent, for

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example, acetone, tetrahydrofuran, 1,2-dimethoxyethane, and the like, followed by the addition of hydrogen in the presence of a catalyst, such as, for example, $\text{Pd}(\text{OH})_2/\text{C}$, Pd/C , $\text{Pd}/\text{Al}_2\text{O}_3$, and the like, in the presence of an acid, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, and the like, to afford the compound of Formula (13). Preferably, the reaction is carried out with sodium hydroxide in benzyl alcohol followed by hydrogenation in the presence of $\text{Pd}(\text{OH})_2/\text{C}$ and sulfuric acid.

The process of the present invention in its second aspect is outlined in Scheme 2. Thus, a compound of Formula (4), prepared as described in Scheme 1, is reacted with a compound of Formula (20) wherein R and M are as defined above and a compound of Formula (7) with removal of water with the aid of a chemical drying agent such as, for example; molecular sieves and the like or with the aid of a Dean-Stark water trap or using azeotropic distillation with a suitable solvent such as, for example tetrahydrofuran, toluene, and the like, to afford a compound of Formula (8) wherein R^1 is as defined above. Preferably, the reaction is carried out with a compound of Formula (20) wherein R is PhCH_2 and M is sodium in the presence of activated 3A molecular sieves in tetrahydrofuran.

The process of the present invention in its third aspect is outlined in Scheme 3. Thus, a compound of Formula (11) is reacted with an acetal of Formula (15) wherein R^5 and R^{5a} are independently the same or different and are, methyl, ethyl, or $-(\text{CH}_2)_n-$ wherein n is an integer of 2 to 4, and R is as defined above in the presence of an acid such as, for example, hydrochloric acid, pyridinium *p*-toluenesulfonate, *p*-toluenesulfonic acid and the like in a solvent such as, for example, toluene, dichloromethane, methyl tertiary butyl ether, and the like, followed by the addition of an aldehyde corresponding to the previous acetal of Formula (15) in the presence of a strong base such as, for example, a non-nucleophilic base, for example, potassium tertiary butoxide, potassium bis(trimethylsilyl) amide, 1,8-diazabicyclo[5.4.0] undec-7-ene and the like, to afford a compound of Formula (14) wherein R^1 and R are as defined above. Preferably, the reaction is carried out with benzaldehyde dimethyl acetal in toluene in the presence of *p*-toluenesulfonic acid followed by the addition of benzaldehyde and potassium tertiary butoxide in tetrahydrofuran.

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A compound of Formula (14) is reacted with hydrogen in the presence of a catalyst such as, for example, palladium on carbon or platinum on carbon and the like in the presence of an acid such as, for example, hydrochloric acid and the like in a solvent such as, for example, toluene, tetrahydrofuran, methyl tertiary butyl ether, ethyl acetate, and the like, and an alcohol, such as, for example, methanol, ethanol, and the like, to afford a compound of Formula (13). Preferably, the reaction is carried out in toluene in the presence of platinum on carbon in the presence of methanol in the presence of hydrochloric acid.

Optionally, a compound of Formula (14) is reacted with an acid such as, for example, hydrochloric acid, pyridinium *p*-toluenesulfonate, *p*-toluenesulfonic acid, and the like, in a solvent such as, for example, toluene, dichloromethane, methyl tertiary butyl ether, and the like to afford the compound of Formula (13). Preferably, the reaction is carried out in methylene chloride in the presence of *p*-toluenesulfonic acid.

Alternatively, a compound of Formula (11) is reacted with an acid, such as, for example, hydrochloric acid, hydrobromic acid, *p*-toluenesulfonic acid, and the like, in a non-nucleophilic solvent, such as, for example, toluene, acetonitrile, methyl tertiary butyl ether, tetrahydrofuran, and the like, to afford a compound of Formula (13). Preferably, the reaction is carried out in toluene in the presence of *p*-toluenesulfonic acid.

The process of the present invention in its fourth aspect is outlined in Scheme 4. Thus, a compound of Formula (10) wherein R^1 is as defined above is reacted with one molar equivalent of hydrogen in the presence of a catalyst using the methodology described above for the conversion of a compound of Formula (10) to a compound of Formula (11) to afford either a compound of Formula (18) or Formula (18a) wherein R^1 is as defined above or a mixture thereof. A mixture of compounds of Formula (18) and (18a) may be separated using conventional methodology, such as, for example, chromatography and the like. Preferably, a mixture of compounds of Formula (18) and (18a) is separated using HPLC.

A compound of Formula (18) or (18a) or a mixture thereof is reacted with hydrogen in the presence of a catalyst as described above for preparing a compound of Formula (11) to afford a compound of Formula (11b) wherein R^{1a}

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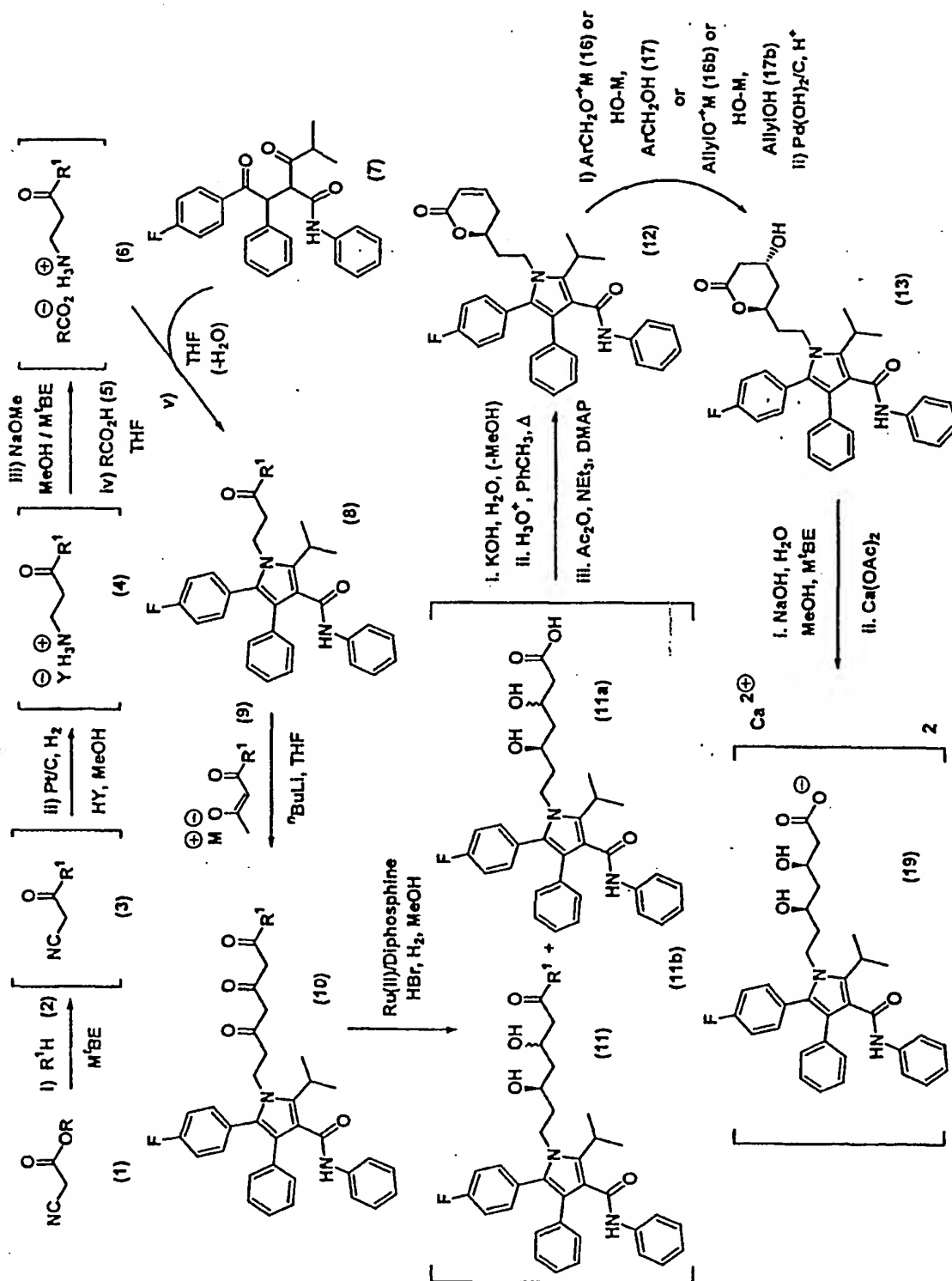
is as defined above. Preferably, the reaction is carried out using at least one molar equivalent of hydrogen.

The compound of Formula (13) can be converted to atorvastatin calcium (19) using the procedures disclosed in United States Patents No. 5,273,995 and
5 5,969,156.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

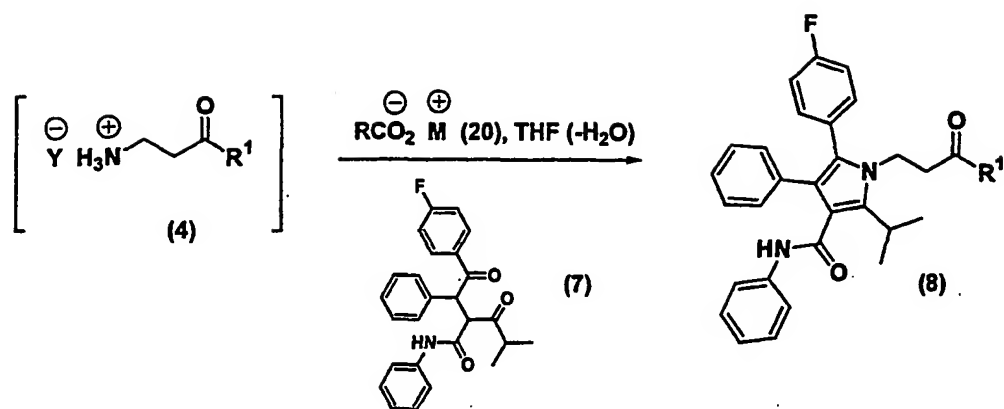
- 31 -

Scheme 1



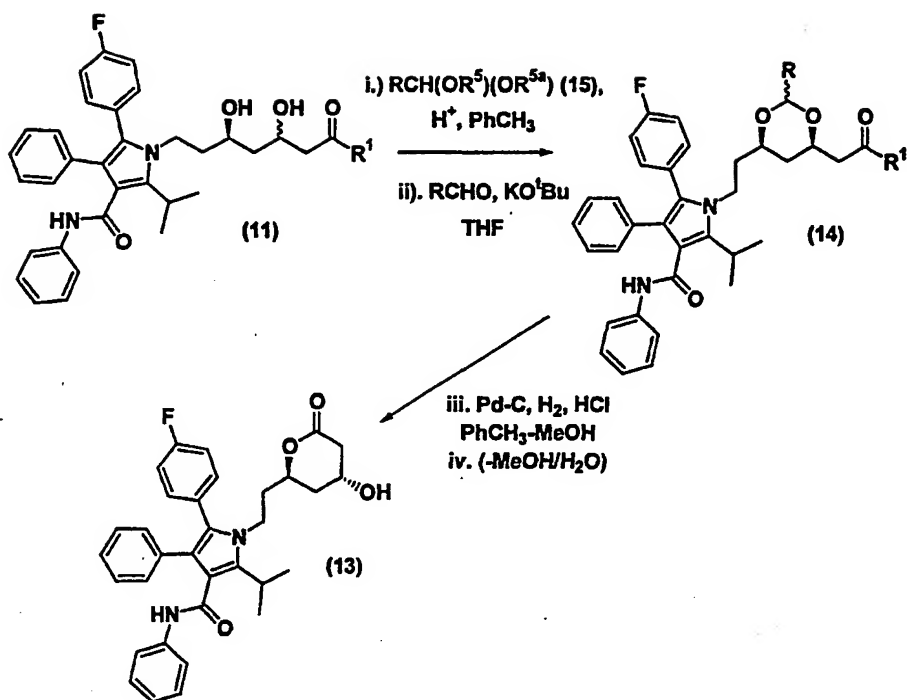
-32-

Scheme 2



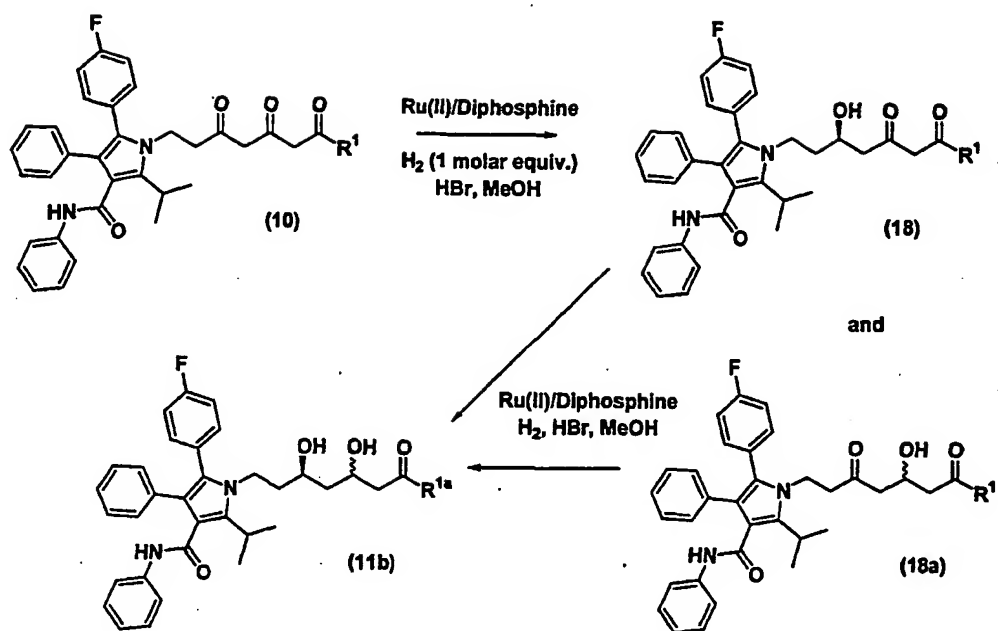
-33-

Scheme 3



-34-

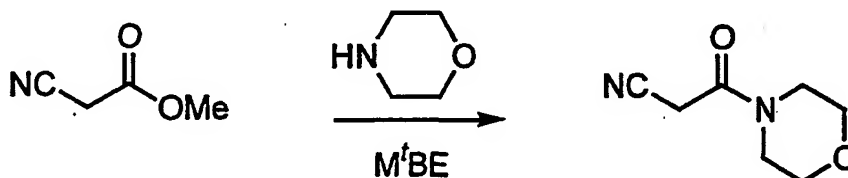
Scheme 4



-35-

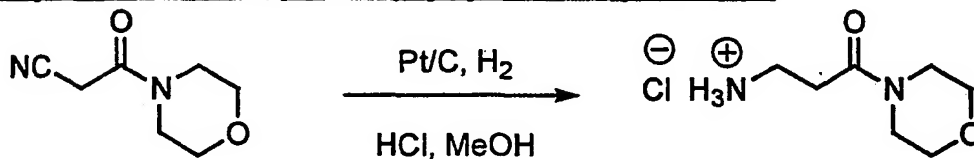
EXAMPLE 1

5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide

Step 1: 3-Morpholin-4-yl-3-oxo-propionitrile

A nitrogen inerted reactor equipped with reflux condenser, nitrogen inlet and mechanical stirring is charged with morpholine (1.2 mol), methyl cyanoacetate (1.0 mol) and MtBE (52 mL). The homogeneous solution is heated to *ca.* 55°C and stirred at that temperature for 12 to 18 hours. MtBE (33 mL) is added over *ca.* 15 minutes, and the solution is slowly cooled below 50°C where nucleation becomes evident. Additional MtBE (66 mL) is added over a 1-hour period. During this time, the reaction is allowed to cool to near ambient temperature. After complete MtBE addition, the reaction is cooled with stirring to *ca.* 0°C. The resulting precipitate is collected *via* filtration and the cake is washed with additional MtBE (*ca.* 40 mL). The solid is dried under vacuum at *ca.* 45°C to provide 3-morpholin-4-yl-3-oxo-propionitrile (139 g). This material is used in subsequent steps without further purification.

m/z (APCI(*m*+1)) 154.9; calcd for C₇H₁₀N₂O₂ 154.07.

Step 2: 3-Amino-1-morpholin-4-yl-propan-1-one; hydrochloride

A nitrogen inerted reactor is charged with 5% Pt-C (43 g; 58% water-wet) followed by 3-morpholin-4-yl-3-oxo-propionitrile (2.8 mol). A solution of MeOH (3.4 L) and 12N HCl (3.08 mol) is added at such a rate as to maintain an internal temperature of *ca.* 25°C. The vessel and its contents are degassed *via* three N₂ pressure purges (50 psi). The atmosphere is switched to hydrogen *via* three H₂ pressure purges (50 psi), and the reaction is stirred vigorously at *ca.* 25°C under a

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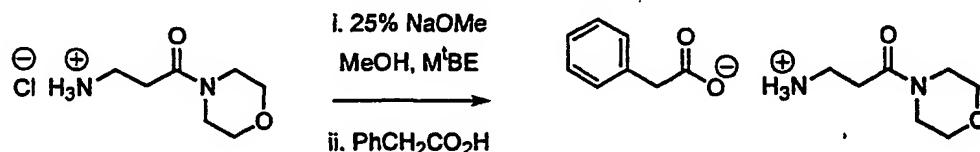
sustained pressure of hydrogen (50 psi) for *ca.* 24 hours. The H₂ pressure is released and replaced with N₂. The reaction is passed through filter agent, which is subsequently washed with MeOH (500 mL). The reaction is concentrated *in vacuo* to a volume of *ca.* 1.4 L, and IPA (2.2 L) is added. The reaction mixture is cooled to 0°C and filtered. The filter cake is washed with MtBE (500 mL) and dried under vacuum at *ca.* 30°C to provide 3-amino-1-morpholin-4-yl-propan-1-one, hydrochloride as a white solid (439 g). This material is used in subsequent steps without further purification.

¹H NMR (400 MHz, DMSO) δ 2.72 (t, 2H, *J* = 6.78), 2.96 (t, 2H, *J* = 6.77), 3.83-3.44 (m, 2H), 3.52-3.58 (m, 2H), 8.08 (bs, 3H).

¹³C NMR (100 MHz, DMSO) δ 168.4, 65.9, 45.1, 41.45, 35.1, 29.6.

Free base: *m/z* (APCI(*m*+1)) 159.2; calcd for C₇H₁₄N₂O₂ 158.11.

Step 3: 3-Amino-1-morpholin-4-yl-propan-1-one; compound with phenylacetic acid



A reactor is charged with 3-amino-1-morpholin-4-yl-propan-1-one; hydrochloride (765 mmol). MeOH (380 mL) is added, and the mixture is stirred vigorously at room temperature for *ca.* 10 minutes. MtBE (380 mL) is added and the resulting slurry is cooled to -10°C, where a 25% (w/w) MeOH solution of NaOMe (765 mmol) is added slowly *via* addition funnel at such a rate as to maintain an internal temperature of *ca.* -10°C. The resulting suspension is stirred vigorously under a N₂ atmosphere as it is allowed to warm to 0°C. Solids are removed *via* filtration, rinsing with additional MtBE (50 mL). Solvent is removed *in vacuo* to provide the free base as a crude oil that is taken up in MtBE (600 mL). The mixture is cooled with vigorous agitation to *ca.* 0°C, where phenylacetic acid (765 mmol) is added slowly as a solution in MtBE (300 mL). The reaction mixture is stirred an additional 10 minutes after complete addition, during which time the product precipitates out of solution. The solids are collected *via* filtration,

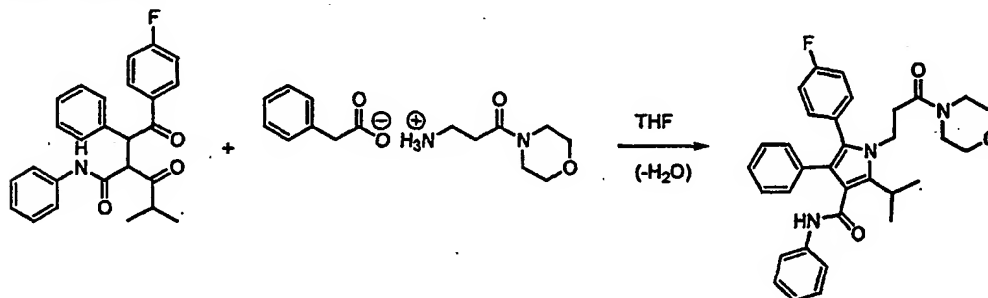
-37-

washed with additional MtBE (100 mL) and dried under vacuum at $\leq 40^\circ\text{C}$ to provide 3-amino-1-morpholin-4-yl-propan-1-one; compound with phenylacetic acid (191 g). This material is carried on to subsequent steps without further purification, or optionally, it can be re-precipitated from MtBE.

- 5 ^1H NMR (400 MHz, DMSO) δ 2.55 (t, 2H, $J = 6.78$), 2.86 (t, 2H, $J = 6.78$) 3.62 (t, 2H), 3.42 (t, 2H), 6.22 (bs, 3H), 7.25-7.12 (m, 5H).
 ^{13}C NMR (100 MHz, DMSO) δ 174.2, 169.0, 138.2, 129.2, 127.8, 125.5, 66.0, 45.2, 44.4, 41.4, 35.7, 31.6.

- 10 Step 4: 5-(4-Fluorophenyl)-2-isopropyl-1-(3-morpholin-4-yl-3-oxo-propyl)-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide

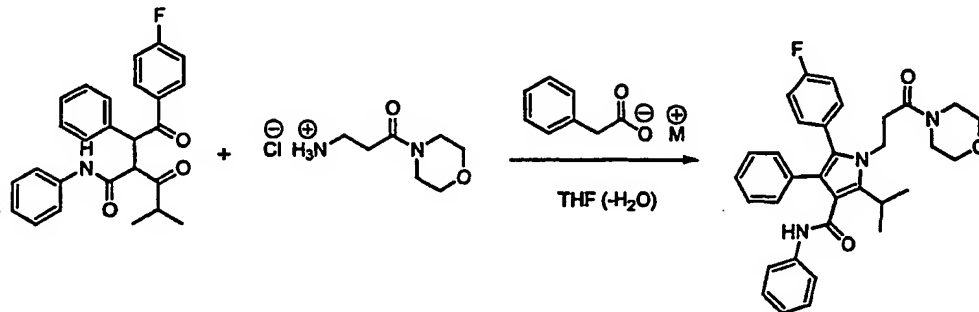
METHOD A



- A nitrogen inerted reactor, equipped with a suitable reflux condenser and soxhlet extractor containing freshly activated 3A molecular sieves (4-8 mesh;
 15 97.2 g), is charged with 3-amino-1-morpholin-4-yl-propan-1-one, compound with phenylacetic acid (765 mmol) and 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide (450 mmol). THF (360 mL) is added, and the resulting solution is stirred vigorously as the reaction is heated at reflux temperature for *ca.* 24 hours, during which time the product begins to precipitate.
 20 Half-saturated aqueous NaHCO_3 (100 mL) is added, and the reaction mixture is cooled with continued stirring to *ca.* 0°C . MtBE (100 mL) is added, and the solids are collected *via* filtration. The solid is washed with distilled water (100 mL) and MtBE (2×100 mL), collected, and dried under vacuum at $\leq 50^\circ\text{C}$ to afford 5-(4-fluorophenyl)-2-isopropyl-1-(3-morpholin-4-yl-3-oxo-propyl)-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide as a white solid (194 g). This material is
 25 carried on to subsequent steps without further purification.

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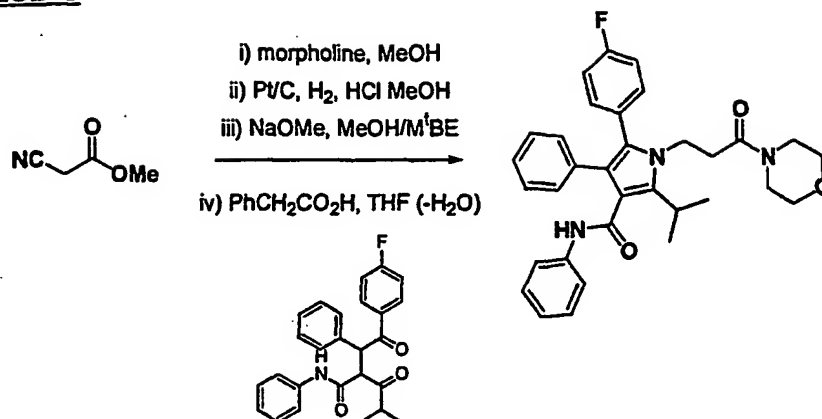
m/z (APCI($m-1$)) 538.2; (APCI($m+1$)) 540.2; calcd for $C_{33}H_{34}FN_3O_3$ 539.26.

METHOD B

A nitrogen inerted reactor, equipped with a suitable reflux condenser and
 5 soxhlet extractor containing freshly activated 3A molecular sieves (4-8 mesh;
 36 g), is charged with 3-amino-1-morpholin-4-yl-propan-1-one hydrochloride
 (170 mmol), phenylacetic acid sodium salt (170 mmol) and 2-[2-(4-fluorophenyl)-
 2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide (100 mmol).
 THF (150 mL) is added, and the resulting solution is stirred vigorously as the
 10 reaction is heated at reflux temperature for *ca.* 24 hours, during which time the
 product begins to precipitate. Aqueous NaHCO_3 (100 mL) is added slowly, and
 the reaction mixture is cooled with continued stirring to *ca.* 0°C . MtBE (100 mL)
 is added, and the solids are collected *via* filtration. The yellow-colored solid is
 washed with distilled water (15 mL) and MtBE (2×15 mL), collected, and dried
 15 under vacuum at $\leq 50^\circ\text{C}$ to afford 5-(4-fluorophenyl)-2-isopropyl-1-(3-morpholin-
 4-yl-3-oxo-propyl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide as a
 white solid (42.1 g). This material is carried on to subsequent steps without further
 purification.

m/z (APCI($m-1$)) 538.2; (APCI($m+1$)) 540.2; calcd for $C_{33}H_{34}FN_3O_3$ 539.26.

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METHOD C

A nitrogen inerted reactor equipped with reflux condenser, nitrogen inlet and mechanical stirring is charged with morpholine (1.2 mol), methyl

5 cyanoacetate (1.0 mol), and MtBE (52 mL). The homogeneous solution is heated to *ca.* 55°C and stirred at that temperature for 12 to 18 hours. MtBE (33 mL) is added over *ca.* 15 minutes, and the solution is slowly cooled below 50°C until nucleation becomes evident. Additional M^tBE (66 mL) is added over a 1-hour period. During this time, the reaction is allowed to cool to near ambient

10 temperature. After complete MtBE addition, the reaction is cooled with stirring to *ca.* 0°C. The resulting precipitate is collected *via* filtration and the cake is washed with additional MtBE (40 mL). The crude 3-morpholin-4-yl-3-oxo-propionitrile is taken up in MeOH (2 L) and transferred to a nitrogen inerted pressure reactor that has been charged with 5% Pt-C (55 g; 58% water-wet). HCl (12 N; 1.1 mol) is

15 added at such a rate as to maintain an internal temperature of *ca.* 25°C. The vessel and its contents are degassed *via* three N₂ pressure purges (50 psi). The atmosphere is switched to hydrogen *via* three H₂ pressure purges (50 psi), and the reaction is stirred vigorously at *ca.* 25°C under a sustained pressure of hydrogen (50 psi) for *ca.* 24 hours. The H₂ pressure is released and replaced with N₂. The

20 reaction is passed through filter agent, which is subsequently washed with MeOH (500 mL). The reaction is concentrated to a MeOH-wet solid, which is reslurried in IPA (100 mL). The slurry is cooled to 0°C and filtered. The filter cake is washed with cold (0°C) IPA (75 mL) and reslurried in MeOH (500 mL) and M^tBE (500 mL). The slurry is cooled with agitation to -10°C where a 25% (w/w)

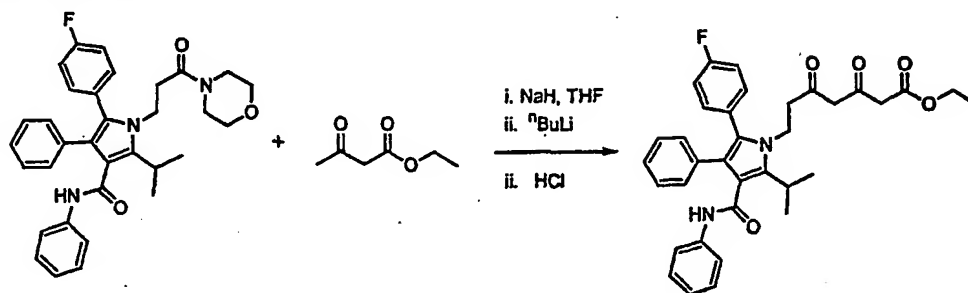
-40-

solution of NaOMe in MeOH (1 mol) is added dropwise at such a rate as to maintain an internal reaction temperature of $\leq 5^{\circ}\text{C}$. The resulting suspension is filtered to afford a clear solution of free base. The solvent is removed *in vacuo* to provide a crude oil that is taken up in THF (450 mL) and cooled to *ca.* 0°C . This solution is transferred into a nitrogen inerted reactor that contains phenylacetic acid (1.0 mol) and 2-[2-(4-fluorophenyl)-2-oxo-1-phenyl-ethyl]-4-methyl-3-oxo-pentanoic acid phenylamide (590 mmol). The reactor is equipped with a suitable reflux condenser and soxhlet extractor containing freshly activated 3A molecular sieves (4-8 mesh; 125 g). The resulting solution is stirred vigorously as the reaction is refluxed under a N_2 atmosphere for *ca.* 24 hours, during which time the product begins to precipitate. Half-saturated aqueous NaHCO_3 (130 mL) is added slowly, and the reaction mixture is cooled with continued stirring to *ca.* 0°C . MtBE (130 mL) is added, and the solids are collected *via* filtration. The solid is washed with distilled water (130 mL) and MtBE (2×130 mL), collected, and dried under vacuum at $\leq 50^{\circ}\text{C}$ to afford 5-(4-fluorophenyl)-2-isopropyl-1-(3-morpholin-4-yl-3-oxo-propyl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide as a white solid (223 g). This material is carried on to subsequent steps without further purification.

m/z (APCI($m-1$)) 538.2; (APCI($m+1$)) 540.2; calcd for $\text{C}_{33}\text{H}_{34}\text{FN}_3\text{O}_3$ 539.26.

Step 5: 7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester

METHOD A



A dry, nitrogen inerted reactor is charged with sodium hydride (300 mmol). Anhydrous THF (150 mL) is added and the resulting mixture is cooled under nitrogen to *ca.* -20°C . Ethyl acetoacetate (307 mmol) is added at

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such a rate as to maintain an internal reaction temperature of $\leq -10^{\circ}\text{C}$. The addition is followed by a THF rinse (30 mL) and the resulting solution is stirred for approximately 45 minutes at $\leq -10^{\circ}\text{C}$. The temperature is allowed to cool to *ca.* -18°C . A 10.0 M solution of *n*-BuLi in hexanes (300 mmol) is added at such a rate as to maintain an internal reaction temperature of $\leq -4^{\circ}\text{C}$. The addition is followed by a THF rinse (30 mL) and the resulting orange solution is stirred for about 90 minutes at $\leq -4^{\circ}\text{C}$. The temperature is allowed to cool to *ca.* -25°C . To the solution of dienolate is added 5-(4-fluorophenyl)-2-isopropyl-1-(3-morpholin-4-yl-3-oxo-propyl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (74 mmol), and the resulting slurry is stirred at *ca.* -23°C for 20 hours. The reaction is quenched into a mixture of 18% aqueous HCl (898 mmol) and MtBE (20 mL) at such a rate as to maintain an internal reaction temperature of $\leq -2^{\circ}\text{C}$. The reactor and transfer system is rinsed with THF (30 mL) and transferred to the reaction mixture. The two-phase solution is allowed to warm to *ca.* 20°C with stirring. The mixture is transferred to a separatory funnel, and the phases are allowed to separate. The organic layer is washed with water (33 mL) and saturated aqueous NaCl (33 mL). All aqueous layers are back-extracted with MtBE (40 mL). The two organic layers are combined and concentrated *in vacuo* to a crude oil maintaining an internal batch temperature of $\leq 60^{\circ}\text{C}$. EtOH (24 mL) is added to the oil and, again, the mixture is concentrated *in vacuo*. EtOH (330 mL) and water (33 mL) are immediately added to the resulting oil, and the solution of product is allowed to stand at $\leq 10^{\circ}\text{C}$ for *ca.* 14 hours. The resulting solid is collected, washed with cold 20% aqueous EtOH (100 mL) and dried *in vacuo* to afford 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester (35.6 g) as a white solid. This material is carried on to subsequent steps without further purification, or optionally, it can be re-precipitated from IPA/H₂O.

HRMS *m/z* (ESI(*m*-1)) 581.2463; calcd for C₃₅H₃₅FN₂O₅ 582.2530.

In a process analogous to Step 5 METHOD A, by substituting the appropriate ester or amide of acetoacetic acid for ethyl acetoacetate, one obtains the following compounds:

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7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *tert*-butyl ester.

HRMS m/z (ESI($m-1$)) 609.2772; APCI($m+1$) 611.3; calcd for $C_{37}H_{39}FN_2O_5$ 610.2843.

5 7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, isopropyl ester.

m/z (DCI($m+1$)) 597; calcd for $C_{36}H_{37}FN_2O_5$ 596.27.

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, methyl ester.

10 m/z (DCI($m+1$)) 569; calcd for $C_{34}H_{33}FN_2O_5$ 568.24.

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, morpholino amide.

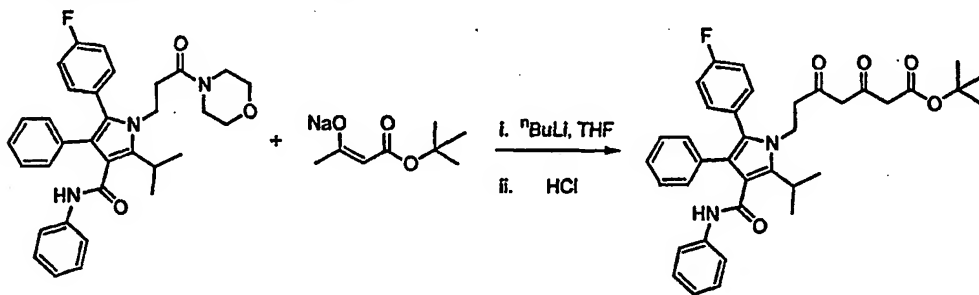
HRMS m/z (ESI($m-1$)) 622.2715; calcd for $C_{37}H_{38}FN_3O_5$ 623.2795.

15 7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *N,N*-dimethyl amide.

m/z (DCI($m+1$)) 582; calcd for $C_{35}H_{36}FN_3O_4$ 581.27.

METHOD B

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *tert*-butyl ester



20

A nitrogen inerted reactor is charged with the sodium salt of *tert*-butyl acetoacetate (100 mmol). Anhydrous toluene (71.5 mL) and THF (8.2 mL, 101 mmol) are added, and the resulting solution is cooled under a positive pressure of nitrogen to *ca.* -10°C. A 10 M hexanes solution of *n*-BuLi (104 mmol)

25 is added at such a rate as to maintain an internal reaction temperature of $\leq 1^\circ\text{C}$. The resulting solution is stirred an additional 20 to 30 minutes after complete

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addition as the temperature is allowed to cool to *ca.* -6°C. Meanwhile, 5-(4-fluorophenyl)-2-isopropyl-1-(3-morpholin-4-yl-3-oxo-propyl)-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (25 mmol) is charged to a second nitrogen inerted reactor. Anhydrous THF (50 mL) is added at room temperature, and the resulting slurry is cooled to *ca.* -10°C and stirred for 15 to 90 minutes. The solution of dienolate is added to the slurry of morpholine amide at such a rate as to maintain an internal reaction temperature *ca.* -5°C. Following this addition, the slurry is stirred at *ca.* -5°C for ≥2 hours. Water (35 mL) is added with vigorous agitation at such a rate as to maintain an internal reaction temperature of ≤0°C.

Concentrated 37% hydrochloric acid (19.0 mL, 229 mmol) is added at such a rate as to maintain an internal reaction temperature of ≤0°C. The two-layered reaction mixture is vacuum distilled, removing >50% of the organic solvents. The distillation is stopped and the lower aqueous layer is discarded. Water (55 mL) is added and the vacuum distillation is continued until a majority of the organic solvents are removed. [Note: It is preferable to drain and replace the aqueous layer before initiating the vacuum distillation.] IPA (100 mL) is added followed by water (100 mL). The mixture is stirred for ≥6 hours, allowing for solidification of the product. The solid is collected *via* filtration, and the cake is washed with pre-mixed 1:1 IPA:H₂O. The resulting solid is dried *in vacuo* at 35°C to provide 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *tert*-butyl ester (14.1 g) as a white solid. This material is carried on to subsequent steps without further purification, or optionally, it can be re-precipitated from toluene.

HRMS *m/z* (ESI(*m*-1)) 609.2772; APCI(*m*+1) 611.3; calcd for C₃₇H₃₉FN₂O₅ 610.2843.

In a process analogous to Step 5 METHOD B, by substituting the sodium salt of the appropriate ester or amide of acetoacetic acid for the sodium salt of *tert*-butyl acetoacetate, one obtains the following compounds:

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester.

HRMS *m/z* (ESI(*m*-1)) 581.2463; calcd for C₃₅H₃₅FN₂O₅ 582.2530.

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7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, isopropyl ester.

m/z (DCI($m+1$)) 597; calcd for $C_{36}H_{37}FN_2O_5$ 596.27.

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, methyl ester.

m/z (DCI($m+1$)) 569; calcd for $C_{34}H_{33}FN_2O_5$ 568.24.

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, morpholino amide.

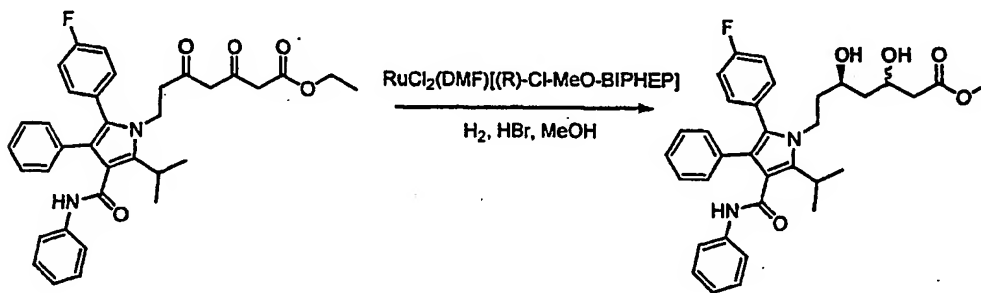
HRMS m/z (ESI($m-1$)) 622.2715; calcd for $C_{37}H_{38}FN_3O_5$ 623.2795.

7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *N,N*-dimethyl amide.

m/z (DCI($m+1$)) 582; calcd for $C_{35}H_{36}FN_3O_4$ 581.27.

Step 6: (5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester

METHOD A



A nitrogen inerted pressure reactor is charged with 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester (100.0 mmol) and MeOH (250 mL). The resulting slurry is heated with stirring to *ca.* 55°C to afford a homogeneous solution. The vessel and its contents are degassed *via* three 50 psi pressure purges with argon. Under a steady flow of argon, 1 M methanolic HBr (7.0 mmol) and the $RuCl_2(DMF)_n[(R)-Cl-MeO-BIPHEP]$ catalyst (0.5 mmol) are added, and the reactor is given an additional 50 psi pressure purge with argon. The atmosphere is switched to hydrogen *via* three 50 psi pressure purges. The reaction is stirred vigorously at 65°C under a

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sustained pressure of hydrogen (50 psi) until hydrogen uptake ceases. The reaction is allowed to cool to ambient temperature, and the hydrogen pressure is released and replaced with nitrogen. The crude MeOH solution of (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester is carried on to subsequent steps without purification, or optionally, it can be isolated *via* flash column chromatography on silica gel, eluting with ethyl acetate-heptane mixtures.

HPLC analysis (YMC ODS AQ S5; 1 mL/min; 30°C; 254 nm: CH₃CN/H₂O, 60:40 (0-22 min) to 100:0 (27-37 min) to 60:40) indicated a *syn:anti* ratio of 1:1.5. Chiral HPLC analysis (Chiralcel OD-H column; 5% EtOH:Hexanes; t_R (3R,5R) = 23.1 min./ t_R (3R,5S) = 18.0 min./ t_R (3S,5S) = 24.8 min./ t_R (3S,5R) = 19.9 min.) indicated an enantiomeric excess at C-5 of $\geq 98\%$, favoring the (R) configuration. m/z (DCI($m+1$)) 573; calcd for C₃₄H₃₇FN₂O₅ 572.27.

In a process analogous to Step 6 METHOD A, using the appropriate alcoholic solvent in place of MeOH, one obtains the following compounds, for example:

(5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, ethyl ester.
 m/z (DCI($m+1$)) 587; calcd for C₃₅H₃₉FN₂O₅ 586.28.

Chiral HPLC analysis (Chiralcel OD-H column; 5% EtOH:Hexanes; t_R (3R,5R) = 17.6 min./ t_R (3R,5S) = 14.7 min./ t_R (3S,5S) = 20.9 min./ t_R (3S,5R) = 15.9 min.) indicated an enantiomeric excess at C-5 of $\geq 98\%$, favoring the (R) configuration.

(5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, isopropyl ester.
 m/z (DCI($m+1$)) 601; calcd for C₃₆H₄₁FN₂O₅ 600.30.

In a process analogous to Step 6 METHOD A, using the appropriate ester or amide from Step 5 in a non-nucleophilic/non-coordinating solvent (e.g., toluene) in place of MeOH, and acetic acid in place of HBr, one can avoid transesterification and obtain the following compounds, for example:

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(5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, *tert*-butyl ester.

m/z (APCI(*m*+1)) 615.3; calcd for C₃₇H₄₃FN₂O₅ 614.32.

5 (5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, morpholino amide.

m/z (APCI(*m*-1+HCO₂H)) 672.3; calcd for C₃₇H₄₂FN₃O₅ 627.31.

(5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, *N,N*-dimethyl amide.

m/z (APCI(*m*+1)) 586; calcd for C₃₅H₄₀FN₃O₄ 585.30.

10 In a process analogous to Step 6 METHOD A, using alternative Ru(II)-chiral diphosphine complexes in place of RuCl₂(DMF)_n[(R)-Cl-MeO-BIPHEP]] as the hydrogenation catalyst, one can obtain the identical products with varying enantiomeric excess at C-5. For example, in the reduction of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester to (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester
15 proceeded as follows:

RuCl₂(DMF)_n[(R)-(+)-BINAP] complex provided product with 90% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

20 RuCl₂(DMF)_n[(R)-(+)-*p*Tol-BINAP] complex provided product with 91% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

RuCl₂(DMF)_n[(R)-(+)-C4-TunaPhos] complex provided product with 93% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

25 RuCl₂(DMF)_n[(R)-(+)-C2-TunaPhos] complex provided product with 98% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

30 RuCl₂(DMF)_n[(S)-(-)-MeO-BIPHEP] complex provided product with 95% *ee* (favoring the (S) configuration) at C-5 as determined by chiral HPLC analysis.

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RuCl₂[(R)-(+)-Cl-MeO-BIPHEP] (NEt₃)_n complex provided product with ≥98% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

5 RuCl₂[(R)-(+)-BINAP] (NEt₃)_n complex provided product with 91% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

RuCl₂[(R)-(+)-*p*Tol-BINAP] (NEt₃)_n complex provided product with 91% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

10 [Ru(TFA)₂((R)-(+)-Cl-MeO-BIPHEP)]_n complex provided product with ≥98% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

[Ru(TFA)₂((R)-(+)-BINAP)]_n complex provided product with 90% *ee* (favoring the (R) configuration) at C-5 as determined by chiral HPLC analysis.

METHOD B

15 A nitrogen inerted pressure reactor is charged with benzene ruthenium (II) chloride dimer (11 mg) and (R)-(+)-C2-TunaPhos (26 mg). The reactor is given a pressure purge with N₂ and N₂-sparged MeOH (1.0 mL) is added *via* syringe. The resulting mixture is thoroughly purged with N₂ and stirred at 25°C for 30 minutes.

20 A solution of 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, *tert*-butyl ester (0.5 g) in N₂-sparged MeOH (4.5 mL) is added to the reactor *via* syringe, and the resulting mixture is allowed to stir under N₂ at 60°C for 30 minutes. The solution is stirred at 60°C under a sustained H₂ pressure of 60 psi for 22 hours. The reaction is cooled to ambient temperature where it is repeatedly purged with N₂. The crude MeOH

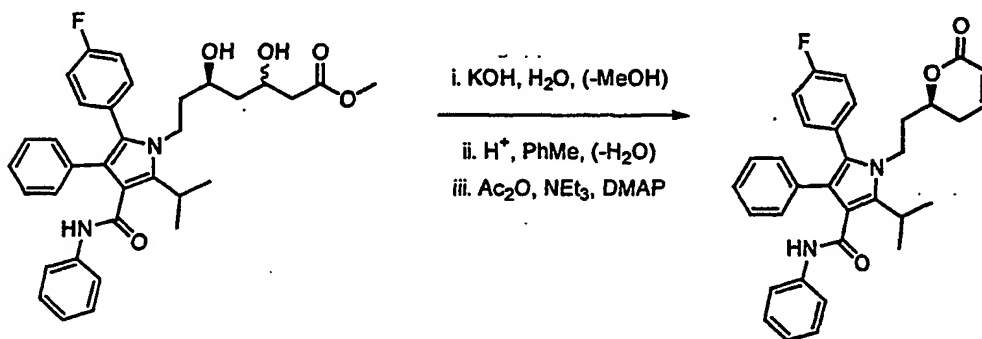
25 solution of (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester is carried on to subsequent steps without purification, or optionally, it can be isolated *via* flash column chromatography on silica gel, eluting with ethyl acetate-heptane mixtures.

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HPLC analysis (YMC ODS AQ S5; 1 mL/min; 30°C; 254 nm: CH₃CN/H₂O, 60:40 (0-22 min.) to 100:0 (27-37 min.) to 60:40) indicated a *syn:anti* ratio of 1:1.4.

Chiral HPLC analysis (Chiralcel OD-H column; 5% EtOH:Hexanes; $t_R(3R,5R)$ = 23.1 min./ $t_R(3R,5S)$ = 18.0 min./ $t_R(3S,5S)$ = 24.8 min./ $t_R(3S,5R)$ = 19.9 min.) indicated an enantiomeric excess at C-5 of $\geq 97\%$, favoring the (R) configuration. m/z (DCI($m+1$)) 573; calcd for C₃₄H₃₇FN₂O₅ 572.27.

Step 7: 5-(4-Fluorophenyl)-2-isopropyl-1-[2-((S)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide



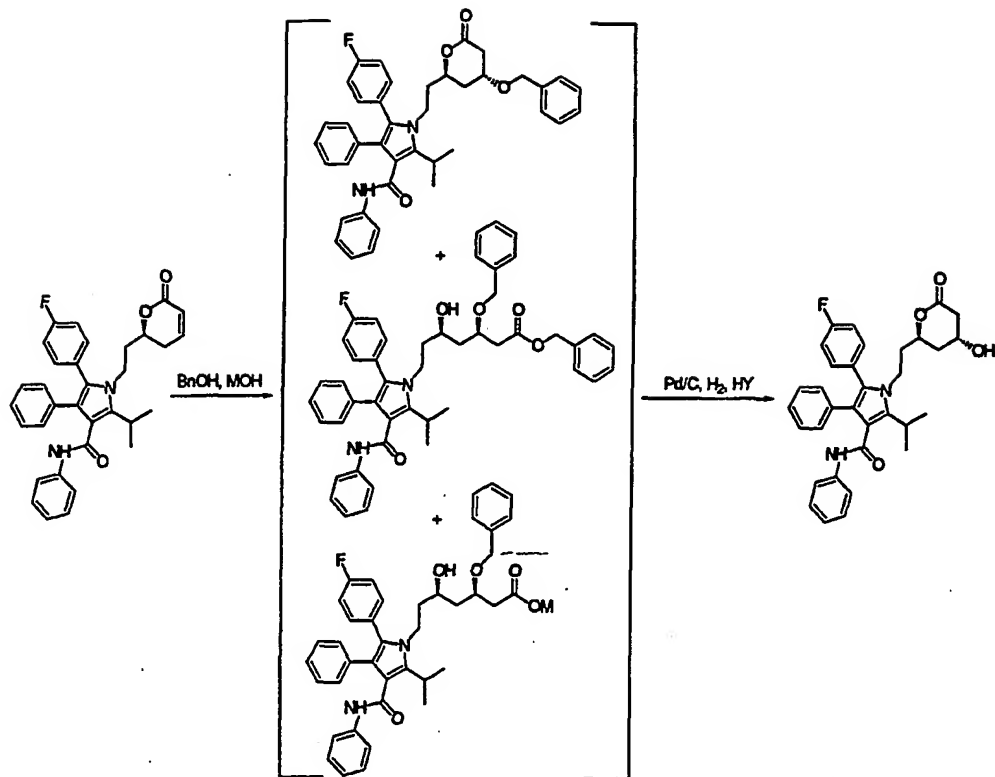
A suitable nitrogen inerted reactor is charged with KOH (110.0 mmol) and water (300 mL). To this rapidly stirring solution is added the crude Step 6 solution of (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester (*ca.* 100 mmol/ $>98\%$ *ee*) in MeOH (250 mL). The mixture is heated under a nitrogen atmosphere to an internal temperature of *ca.* 85°C. During this time, MeOH is removed *via* distillation. The resulting reaction mixture is allowed to cool to 45°C, where it is washed with MtBE (2x150 mL). The MtBE phases are separated and discarded. To the 45°C aqueous phase is added toluene (125 mL), followed by a slow addition of 6N HCl (20 mL). The two-phase mixture is stirred for 10 minutes, and the layers are separated. The aqueous phase is extracted with a second portion of toluene (125 mL) and discarded. The combined organics are heated to reflux under a nitrogen atmosphere. During this time, 130 mL of distillate is collected and discarded. The resulting solution is cooled to *ca.* 60°C, where NEt₃ (140 mmol),

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- DMAP (2.0 mmol) and Ac₂O (70.0 mmol) are added successively at such a rate as to maintain an internal reaction temperature of 55°C to 65°C. This solution is stirred for *ca.* 1.5 hrs at 60°C. The mixture is cooled to 50°C, where 1N HCl (100 mL) is added slowly. The two-phase mixture is stirred for 10 minutes, the phases are separated, and the aqueous phase discarded. The organic phase is washed with second portions of 1N HCl (100 mL) and water (100 mL) while maintaining a temperature of 45°C to 55°C. The toluene solution is diluted with Bu₂O (200 mL) and the resulting solution is slowly cooled to 0°C with continuous agitation. The resulting solid is collected on a filter funnel and dried under vacuum to provide 5-(4-fluorophenyl)-2-isopropyl-1-[2-((S)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide as a white to off-white solid (34.4 g). This material is carried on to subsequent steps without further purification, or optionally, it can be re-precipitated from IPA/H₂O. *m/z* (DCI(*m*+1)) 523; calcd for C₃₃H₃₁FN₂O₃ 522.23.
- Chiral HPLC analysis (Chiralpak AD column; 1 mL/min; 30°C; 254 nm; 10% IPA:Hexanes; *t_R*(R) = 18 min./*t_R*(S) = 16 min.) indicated an enantiomeric excess of >98%, favoring the (R) configuration.

Step 8: 5-(4-Fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide

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METHOD A

An argon-purged reactor is charged with 5-(4-fluorophenyl)-2-isopropyl-1-[2-((S)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide (0.020 mol/>99% *ee*) and benzyl alcohol (52 mL). The reaction mixture is cooled to -10°C and NaOH (0.040 mol) is added. After stirring for 19 hours at -10°C the reaction is quenched with 37% HCl (0.042 mol) and diluted with water (25 mL) and toluene (25 mL). After the mixture is warmed to ambient temperature, the lower aqueous layer is discarded. The upper organic layer is combined with 20% Pd(OH)₂/C (1.0 g) and H₂SO₄ (0.01 moles) and hydrogenated under 50 psi hydrogen at 50°C for 16 hours. The reaction mixture is heated to 80°C and filtered through diatomaceous earth. The reactor and catalyst cake is rinsed with hot toluene (10 mL). The lower aqueous layer is discarded. The upper organic layer is washed with a warm solution of aqueous HCl (0.16 g 37% HCl in 25 mL hot water) and heated to reflux for 2.5 hours under argon, removing water azeotropically. The reaction mixture is cooled to 65°C and seeded with 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-

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ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide. After 2 hours the reaction mixture is allowed to slowly cool to ambient temperature. The resulting slurry is cooled to about 0°C. The product is collected and washed with cold toluene (25 mL). The resulting solid is dissolved in hot toluene (95 mL) and cooled to 65°C and held for 2 hours. The reaction mixture is slowly cooled to ambient temperature and further cooled to 0°C. The product is collected, washed with cold toluene (25 mL) and dried *in vacuo* at 70°C overnight to afford 5-(4-fluorophenyl)-1-[2-((2*R*,4*R*)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (8.4 g) as a white solid.

HPLC analysis (YMC ODS AQ S5; 1 mL/min; 30°C; 254 nm; CH₃CN/H₂O, 60:40 (0-22 min.) to 100:0 (27-37 min.) to 60:40) indicated an *anti:syn* ratio of >99:1.

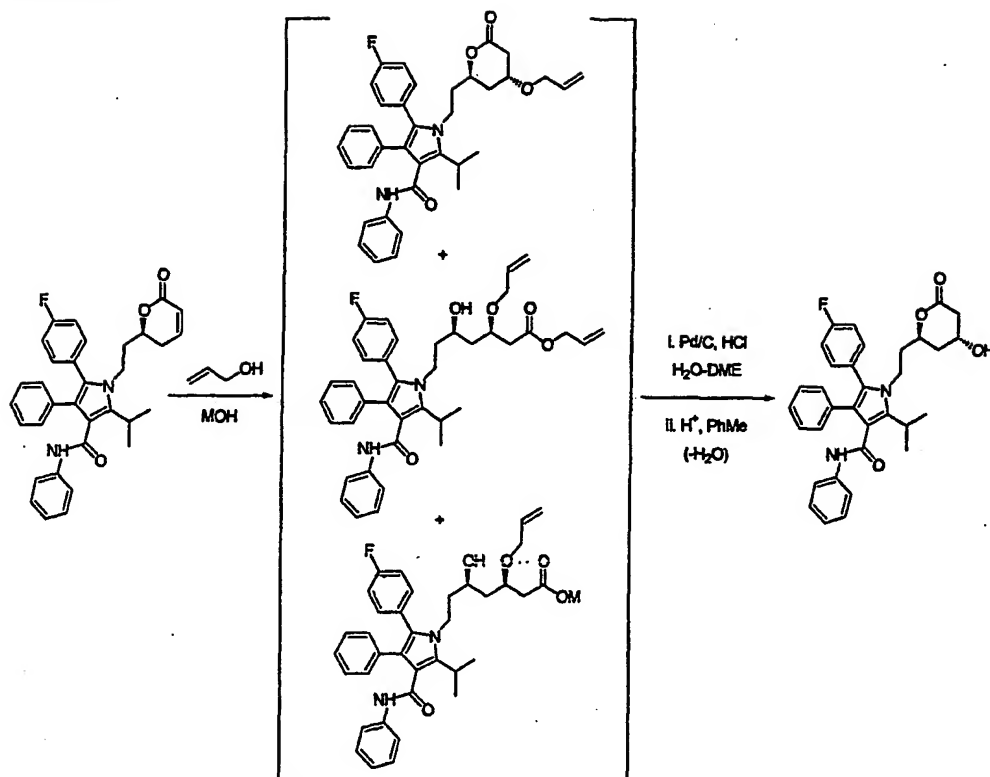
Chiral HPLC analysis (Chiralcel OF; 1 mL/min; 60°C; 254 nm; 20%

IPA:Hexanes; *t_R*(3*R*,5*R*) = 26 min./*t_R*(3*R*,5*S*) = 59 min./*t_R*(3*S*,5*S*) = 33 min./*t_R*(3*S*,5*R*) = 37 min.) indicated an enantiomeric excess at C-5 of >99%, favoring the (*R*) configuration.

m/z (DCI(*m*+1)) 541; calcd for C₃₃H₃₃FN₂O₄ 540.24.

In a process analogous to Step 8 METHOD A, substituted benzylic alcohol derivatives (e.g., *p*-methoxy-benzyl alcohol) may be used in place of benzyl alcohol to afford the corresponding compounds.

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METHOD B

- An argon-purged reactor is charged with 5-(4-fluorophenyl)-2-isopropyl-1-[2-((S)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-ethyl]-4-phenyl-1H-pyrrole-3-
- 5 carboxylic acid phenylamide (19.1 mmol/>99% *ee*) and allyl alcohol (50 mL). The reaction mixture is cooled to -5°C and LiOH (38.2 mmol) is added. After stirring for 1 hour at -5°C the reaction is quenched with 37% HCl (42 mmol) and toluene (125 mL). After the mixture is warmed to ambient temperature, the reaction is concentrated to a volume of *ca.* 75 mL. Additional toluene (50 mL) is
- 10 added and the reaction is concentrated *via* distillation to a crude oil that solidifies upon standing. The crude residue is taken up in DME (340 mL). To this solution is added deionized water (20 mL), *p*-toluenesulfonic acid (2.25 g) and 5% Pd/C (11 g; 50% water-wet). The resulting mixture is heated to 45°C under a N₂
- atmosphere for 1.5 hours and at ambient temperature for an additional 16 hours.
- 15 The solution is passed through filter aid to remove catalyst, and solvent is removed *in vacuo*. The residue is taken up in toluene (50 mL). Water (75 mL) and KOH (950 mg) are added, and the reaction mixture is heated to 65°C where the layers are separated. The aqueous phase is washed with toluene (25 mL) at 65°C

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and the combined toluene layers are discarded. To the aqueous phase is added toluene (50 mL), followed by 6N HCl (3.8 mL). The mixture is stirred vigorously at 65°C for 5 minutes and the phases are separated. The toluene phase is heated to reflux for 2.5 hours under argon, removing water azeotropically. The reaction mixture is cooled to 65°C and seeded with 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide. After 2 hours the reaction mixture is allowed to slowly cool to ambient temperature. The resulting slurry is cooled to about 0°C. The product is collected and washed with cold toluene (25 mL). The resulting solid is dissolved in hot toluene (95 mL) and cooled to 65°C and held for 2 hours. The reaction mixture is slowly cooled to ambient temperature and further cooled to 0°C. The product is collected, washed with cold toluene (25 mL) and dried *in vacuo* at 70°C overnight to afford 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide as a white solid.

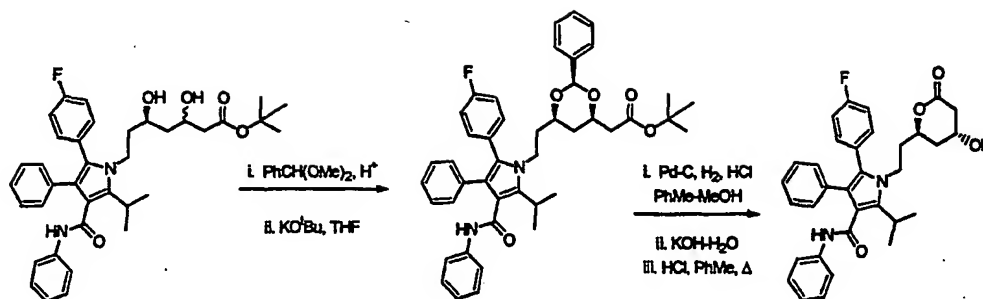
HPLC analysis (YMC ODS AQ S5; 1 mL/min; 30°C; 254 nm; CH₃CN/H₂O, 60:40 (0-22 min) to 100:0 (27-37 min) to 60:40) indicated an *anti:syn* ratio of >99:1.

Chiral HPLC analysis (ChiralCel OF; 1 mL/min; 60°C; 254 nm; 20% IPA:Hexanes; $t_R(3R,5R) = 26$ min./ $t_R(3R,5S) = 59$ min. $t_R(3S,5S) = 33$ min./ $t_R(3S,5R) = 37$ min.) indicated an enantiomeric excess at C-5 of >99%, favoring the (R) configuration.

m/z (DCI($m+1$)) 541; calcd for C₃₃H₃₃FN₂O₄ 540.24.

In a process analogous to Step 8 METHOD B, allylic alcohol derivatives (e.g., crotyl alcohol) may be used in place of allyl alcohol to afford the corresponding compounds.

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METHOD COPERATION A

- A nitrogen inerted reactor is charged with (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, *tert*-butyl ester (10.0 mmol), benzaldehyde dimethyl acetal (44.0 mmol), toluene (40 mL) and *p*-toluenesulfonic acid monohydrate (1.0 mmol). The reaction is stirred vigorously under vacuum for *ca.* 20 hours, or until complete reaction as determined by analysis of an aliquot by HPLC. The solution is cooled under a nitrogen atmosphere to *ca.* -5°C where a 1M THF solution of KOtBu (9.0 mmol) is added in three equal portions, separated by 30 to 45 minutes. The resulting solution is allowed to stir an additional 12 to 14 hours at 0°C. The reaction is quenched by the slow addition of 1N HCl (10 mL). The resulting two-phase mixture is allowed to warm to *ca.* 15°C and is transferred to a separatory funnel where the aqueous phase is removed and discarded. The organic phase is washed with saturated aqueous NaCl (100 mL), dried over anhydrous MgSO₄ (25 g), filtered and concentrated *in vacuo* to a crude oil. This material is carried on to subsequent steps without purification, or optionally, it can be re-precipitated from ether/hexanes.
- m/z* (APCI(*m*+1)) 703.4; calcd for C₄₄H₄₇FN₂O₅ 702.35.

In a process analogous to Step 8 METHOD C OPERATION A using the appropriate ester from Step 6 in place of (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, *tert*-butyl ester, one obtains the following compounds, for example:

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((4R,6R)-6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-ethyl}-2-phenyl-[1,3]dioxan-4-yl)-acetic acid methyl ester.

5 ((4R,6R)-6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-ethyl}-2-phenyl-[1,3]dioxan-4-yl)-acetic acid ethyl ester.

((4R,6R)-6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-ethyl}-2-phenyl-[1,3]dioxan-4-yl)-acetic acid isopropyl ester.

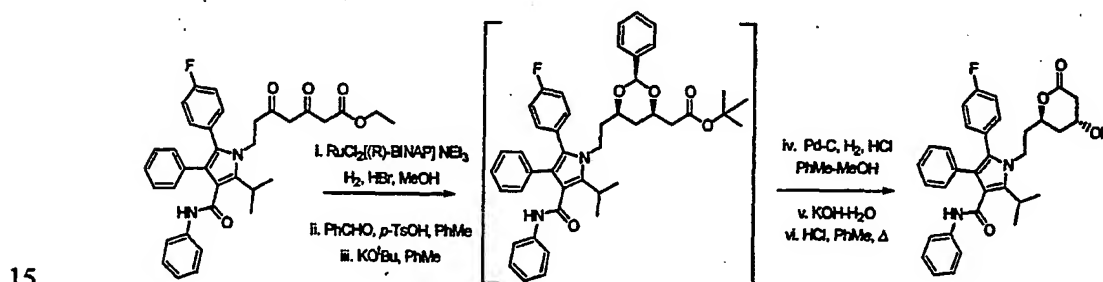
10 OPERATION B

A nitrogen inerted pressure reactor is charged with ((4R,6R)-6-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-ethyl}-2-phenyl-[1,3]dioxan-4-yl)-acetic acid *tert*-butyl ester from OPERATION A (5.0 g), 5% Pd/C (0.45 g; 50% H₂O-wet), 2N HCl in MeOH (1.9 mL), toluene (11 mL),
15 and MeOH (3.1 mL). The vessel and its contents are degassed *via* two cycles of partial evacuation and nitrogen pressurization (25 mm Hg and 50 psi, respectively). The atmosphere is switched to hydrogen *via* three cycles of partial evacuation and hydrogen pressurization (25 mm Hg and 50 psi, respectively). The reaction is stirred vigorously at 40°C under a positive pressure of H₂ (*ca.* 50 psi)
20 for *ca.* 2.5 hours. The reaction is allowed to cool to ambient temperature, and the hydrogen pressure is released and replaced with nitrogen. The reaction is passed through filtering agent to remove the catalyst, rinsing thoroughly with MeOH (2 × 5 mL). To this solution is added KOH (0.6 g) in water (25 mL). The reaction is stirred vigorously under a nitrogen atmosphere and heated to an internal reaction
25 temperature of *ca.* 90°C, removing MeOH *via* distillation. The two-phase mixture is allowed to cool to 70°C and the upper toluene phase is separated and discarded. The aqueous phase is washed with a second portion of toluene (10 mL) at 70°C. This organic wash is also separated and discarded. To the aqueous phase is added toluene (10 mL), followed by a slow addition of 2N HCl (5 mL). The two-phase
30 mixture is stirred for 10 minutes and the layers are separated. The aqueous phase is extracted with a second portion of toluene (10 mL) and is discarded. The

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combined organics are heated to reflux under a Dean-Stark water trap for 2.5 hours under argon. The reaction mixture is cooled to 65°C and seeded with 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide. After 2 hours the reaction mixture is allowed to slowly cool to ambient temperature. The resulting slurry is cooled to *ca.* 0°C. The product is collected and washed with cold toluene (5 mL). The resulting solid is dissolved in hot toluene (20 mL) and cooled to 65°C and held for 2 hours. The reaction mixture is slowly cooled to ambient temperature and then to 0°C. The product is collected, washed with cold toluene (5 mL) and dried *in vacuo* at 70°C overnight to afford 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide as a white solid.

m/z (DCI($m+1$)) 541; calcd for $C_{33}H_{33}FN_2O_4$ 540.24.

METHOD D

A nitrogen inerted pressure reactor is charged with 7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dioxo-heptanoic acid, ethyl ester (100.0 mmol) and EtOH (250 mL). The resulting slurry is heated with stirring to *ca.* 55°C to afford a homogeneous solution. The vessel and its contents are degassed *via* three 50 psi pressure purges with argon. Under a steady flow of argon, 1 M ethanolic HBr (7.0 mmol) and the $RuCl_2[(R)-BINAP] NEt_3$ catalyst (0.5 mmol) are added, and the reactor is given an additional 50 psi pressure purge with argon. The atmosphere is switched to hydrogen *via* three 50 psi pressure purges. The reaction is stirred vigorously at 65°C under a sustained pressure of hydrogen (50 psi) until H_2 uptake ceases. The reaction is allowed to cool to *ca.* 50°C, where the hydrogen pressure is released and replaced with nitrogen. The

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crude EtOH solution of (5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester is diluted with toluene (250 mL). To this solution is added benzaldehyde (150 mmol) and *p*-TsOH monohydrate (5 mmol). The resulting reaction mixture is

5 heated to a pot temperature of 110°C, removing EtOH and water *via* their toluene azeotropes. The solution is cooled under a nitrogen atmosphere to *ca.* -5°C where a 1 M THF solution of K^tBu (90 mmol) is added in three equal portions, separated by 30 to 45 minutes. The resulting solution is allowed to stir an additional 12 to 14 hours at 0°C. The reaction is quenched by the slow addition of

10 1N HCl (100 mL). The resulting two-phase mixture is allowed to warm to *ca.* 15°C and is transferred to a separatory funnel where the aqueous phase is removed and discarded. The organic phase is washed with saturated aqueous NaCl (25 mL), dried over anhydrous MgSO₄ (5 g), filtered and concentrated *in vacuo* to a crude oil that is taken up in MeOH (200 mL). This solution is transferred to a nitrogen

15 inerted pressure reactor containing 5% Pd/C (5 g; 50% water-wet). Concentrated HCl (2 mL) is added and the reaction is stirred under a sustained pressure of H₂ (50 psi) for *ca.* 3 hours at 50°C. The reaction mixture is cooled to ambient temperature, the H₂ is replaced by N₂, and the catalyst is removed *via* filtration. This solution of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-

20 phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, methyl ester is transferred to a nitrogen inerted reactor charged with KOH (110.0 mmol) and water (300 mL). The mixture is heated under a nitrogen atmosphere to an internal temperature of *ca.* 85°C. During this time, MeOH is removed *via* distillation. The resulting reaction mixture is allowed to cool to 45°C, where it is washed with

25 M^tBE (2 × 150 mL). The M^tBE phases are separated and discarded. To the 45°C aqueous phase is added toluene (125 mL), followed by a slow addition of 6N HCl (20 mL). The two-phase mixture is stirred for 10 minutes and the layers are separated. The aqueous phase is extracted with a second portion of toluene (125 mL) and is discarded. The combined organics are heated to reflux under a

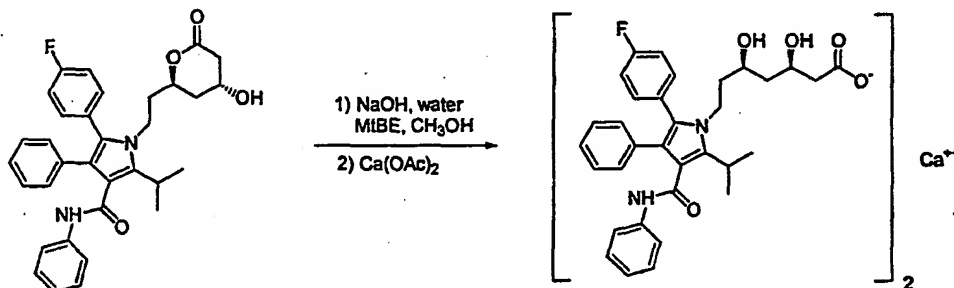
30 Dean-Stark water trap for 2.5 hours under argon. The reaction mixture is cooled to 65°C and seeded with 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-

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tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide. After 2 hours the reaction mixture is allowed to slowly cool to ambient temperature. The resulting slurry is cooled to *ca.* 0°C. The product is collected and washed with cold toluene (100 mL). The resulting solid is dissolved in hot toluene (350 mL) and cooled to 65°C where it is held for 2 hours. The reaction mixture is slowly cooled to ambient temperature and then to 0°C. The product is collected, washed with cold toluene (100 mL) and dried *in vacuo* at 70°C to afford 5-(4-fluorophenyl)-1-[2-((2*R*,4*R*)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide as a white solid.

m/z (DCI(*m*+1)) 541; calcd for C₃₃H₃₃FN₂O₄ 540.24.

Step 9: (R,R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, calcium salt.



An argon-purged reactor is charged with 5-(4-fluorophenyl)-1-[2-((2*R*,4*R*)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylic acid phenylamide (14.8 mmol), MtBE (45 mL) and MeOH (20 mL). A solution of NaOH (15.2 mmol) in water (103 mL) is added and the reaction mixture heated to 52°C. After heating for *ca.* 1 hour, the reaction mixture is cooled to 34°C and the layers are allowed to separate. The upper organic layer is discarded. The lower aqueous layer is washed with MtBE (33 mL) at *ca.* 33°C. The lower aqueous layer is diluted with MtBE (2 mL) and heated to 52°C under argon. A warm solution of Ca(OAc)₂·H₂O (7.5 mmol) in water (44 mL) is added over *ca.* 2 hours. About 5 minutes after the start of the Ca(OAc)₂ addition, the reaction mixture is seeded with a slurry of (R,R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-

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dihydroxy-heptanoic acid, calcium salt (0.08 mmol) in water (1.2 mL) and methanol (0.4 mL). After the $\text{Ca}(\text{OAc})_2$ addition is complete, the reaction mixture is held for *ca.* 15 minutes at 52°C and cooled to 20°C. The product is collected, washed sequentially with a 2:1 solution of aqueous methanol (48 mL) and water (49 mL). After drying *in vacuo* at 70°C, (R,R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid, calcium salt (8.7 g) is obtained as a white solid. The analytical specifications of this material are in agreement with the values reported in the prior art.

PREPARATION OF CATALYSTS

10

EXAMPLE A

$\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-Cl-MeO-BIPHEP}]$ complex

A suitable reaction flask is charged with DMF (17.5 mL). The vessel and its contents are degassed *via* two cycles of partial evacuation and nitrogen pressurization (25 mm Hg and 10 psi, respectively). The excess nitrogen pressure is released, and benzene ruthenium(II) chloride dimer (0.50 mmol) and (R)-(+)-Cl-MeO-BIPHEP (1.10 mmol) are added in rapid succession. The vessel and its contents are again degassed *via* two cycles of partial evacuation and nitrogen pressurization (25 mm Hg and 10 psi, respectively). The excess nitrogen pressure is released, and the reactor is heated to *ca.* 100°C for 10 minutes. The resulting solution is allowed to cool to $\leq 50^\circ\text{C}$ where solvent is removed *in vacuo*, affording $\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-Cl-MeO-BIPHEP}]$ as a rusty-brown solid. The crude complex is used directly in subsequent reactions without purification or unambiguous characterization, or optionally, can be stored under an inert atmosphere for future use.

25

In a process analogous to EXAMPLE A using the appropriate chiral diphosphine ligand in place of (R)-(+)-Cl-MeO-BIPHEP, the following complexes can be obtained, for example:

$\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-BINAP}]_n$ complex.

$\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-}p\text{Tol-BINAP}]_n$ complex.

-60-

$\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-C4-TunaPhos}]_n$ complex.

$\text{RuCl}_2(\text{DMF})_n[(R)-(+)\text{-C2-TunaPhos}]_n$ complex.

$\text{RuCl}_2(\text{DMF})_n[(S)-(-)\text{-MeO-BIPHEP}]_n$ complex.

EXAMPLE B

5 $\text{RuCl}_2[(R)-(+)\text{-BINAP}](\text{NEt}_3)_n$ complex

A nitrogen inerted pressure reactor is charged with dichloro-(1,5-cyclooctadiene)-ruthenium (II) dimer (0.15 mmol) and (R)-(+)-BINAP (0.32 mmol). Toluene (8.0 mL) is added, followed by triethylamine (4.5 mmol). The vessel and its contents are degassed *via* two cycles of partial evacuation and
 10 nitrogen pressurization (25 mm Hg and 10 psi, respectively). The excess nitrogen pressure is released, and the reactor is sealed and heated to *ca.* 140°C where it is maintained for *ca.* 4 hours. The resulting clear red solution is allowed to cool to $\leq 40^\circ\text{C}$ where solvent is removed *in vacuo*, affording $\text{RuCl}_2[(R)-(+)\text{-BINAP}](\text{NEt}_3)_n$ complex as a rusty-brown solid. The crude complex is used directly in
 15 subsequent reactions without purification or unambiguous characterization, or optionally, can be stored under an inert atmosphere for future use.

In a process analogous to EXAMPLE B using the appropriate chiral diphosphine ligand in place of (R)-(+)-BINAP, the following complexes can be obtained, for example:

20 $\text{RuCl}_2[(R)-(+)\text{-Cl-MeO-BIPHEP}](\text{NEt}_3)_n$ complex.

$\text{RuCl}_2[(R)-(+)\text{-BINAP}](\text{NEt}_3)_n$ complex.

$\text{RuCl}_2[(R)-(+)\text{-}p\text{Tol-BINAP}](\text{NEt}_3)_n$ complex.

EXAMPLE C

$[\text{Ru}(\text{TFA})_2((R)-(+)\text{-Cl-MeO-BIPHEP})]_n$ complex

25 A suitable reaction flask is charged with acetone (50 mL). The vessel and its contents are degassed *via* two cycles of partial evacuation and argon pressurization (25 mm Hg and 10 psi, respectively). The excess argon pressure is released, and (0.50 mmol) and (R)-(+)-Cl-MeO-BIPHEP (0.51 mmol) are added in rapid succession. The vessel and its contents are again degassed *via* two cycles

-61-

of partial evacuation and argon pressurization (25 mm Hg and 10 psi, respectively). The excess argon pressure is released, and the reactor is stirred vigorously at *ca.* 30°C. Trifluoroacetic acid (1.2 mmol) is added *via* syringe and the reaction mixture is stirred for an additional 1-hour period. Solvent is removed
5 *in vacuo*, with careful omission of O₂, to afford [Ru(TFA)₂((R)-(+)-Cl-MeO-BIPHEP)]_n complex as a solid. The crude complex is used directly in subsequent reactions without purification or unambiguous characterization, or optionally, can be stored under an inert atmosphere for future use.

In a process analogous to EXAMPLE C using the appropriate chiral
10 diphosphine ligand in place of (R)-(+)-Cl-MeO-BIPHEP, the following complexes can be obtained, for example:

[Ru(TFA)₂((R)-(+)-MeO-BIPHEP)]_n complex.

[Ru(TFA)₂((R)-(+)-BINAP)]_n complex.

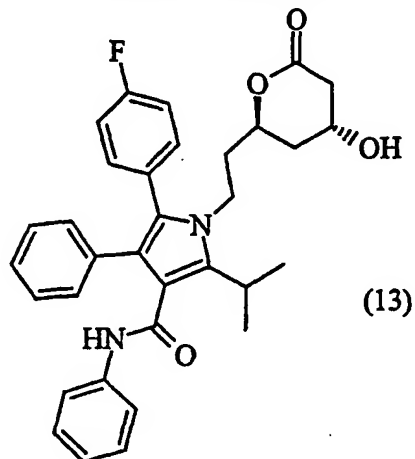
[Ru(TFA)₂((R)-(+)-*p*Tol-BINAP)]_n complex.

-62-

CLAIMS

What is claimed is:

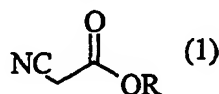
1. A process for the preparation of a compound of Formula (13)



(13)

5 which comprises:

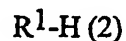
Step (a) reacting a compound of Formula (1)



(1)

wherein R is alkyl, aryl, arylalkyl, or heteroaryl in a solvent with a compound of Formula (2)

10



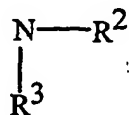
wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is

15



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

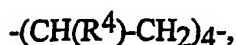
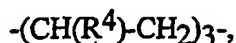
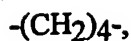
arylalkyl, or

aryl, or

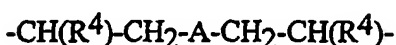
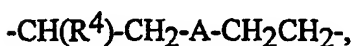
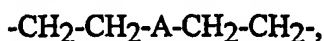
20

R^2 and R^3 together are

-63-



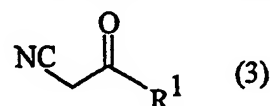
5



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wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and

R is as defined above to afford a compound of Formula (3)



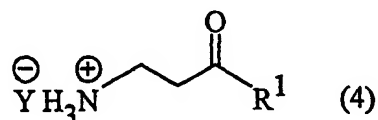
wherein R^1 is as defined above;

Step (b) reacting a compound of Formula (3) with hydrogen in the

15

presence of a catalyst and a strong acid in a solvent to afford a

compound of Formula (4)

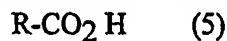


wherein Y is Cl, Br, TsO, MsO, or HSO_4 , and R^1 is as defined above;

Step (c) reacting a compound of Formula (4) with a base in a solvent

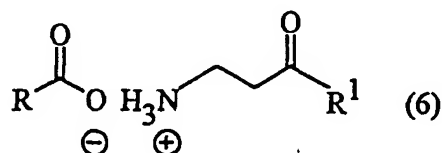
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followed by the addition of a compound of Formula (5)



wherein R is as defined above in a solvent to afford a compound of

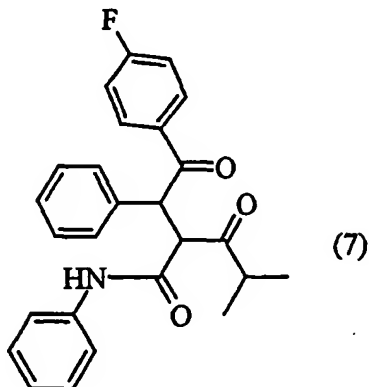
Formula (6)



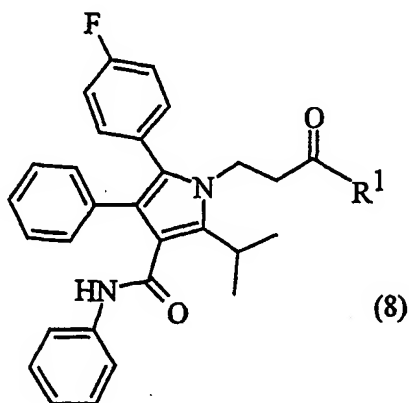
-64-

wherein R and R¹ are as defined above;

Step (d) reacting a compound of Formula (6) with Compound (7)

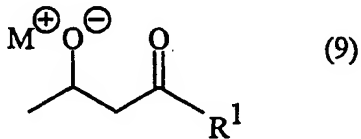


in a solvent with removal of water to afford a compound of Formula (8)



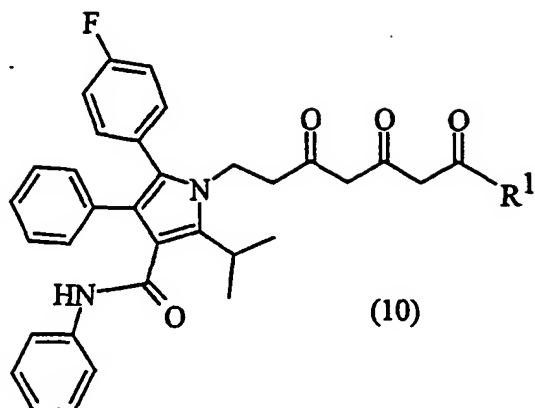
wherein R¹ is as defined above;

Step (e) reacting a compound of Formula (8) with a compound of Formula (9)



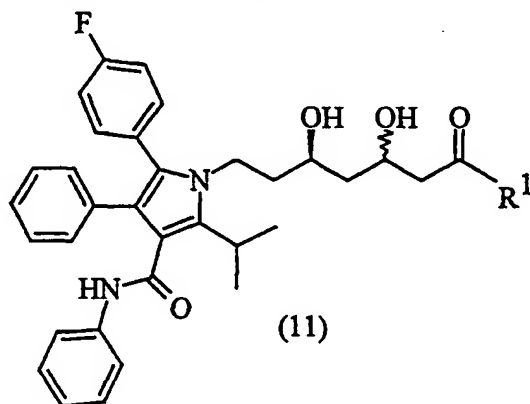
wherein M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum, and R¹ is as defined above in a solvent in the presence of a strong base to afford a compound of Formula (10)

-65-

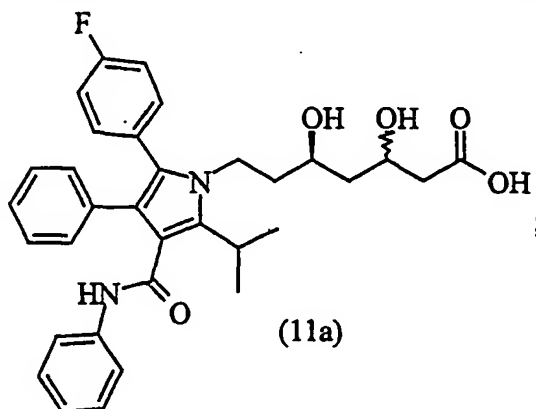


wherein R¹ is as defined above;

Step (f) reacting a compound of Formula (10) with hydrogen in the presence of a catalyst in a solvent in the presence of an acid to afford a compound of Formula (11)

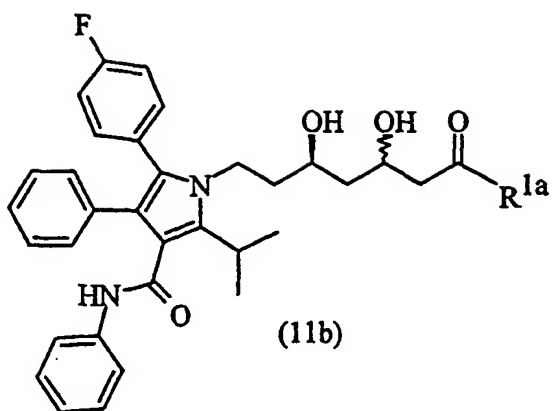


wherein R¹ is as defined above or a compound of Formula (11a)



Step (g) reacting a compound of Formula (11b)

-66-

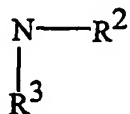


wherein R^{1a} is OH, XR wherein

X is O,

S, or

Se, or R^{1a} is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

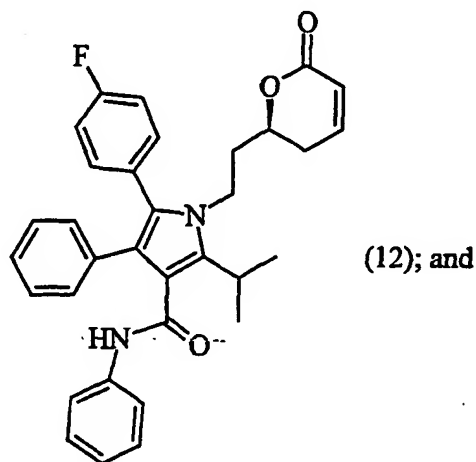
$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

-67-

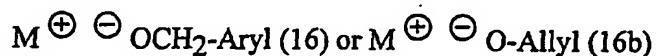
wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N and R is alkyl, aryl, arylalkyl, or heteroaryl in a solvent in the presence of an acid, followed by reaction with a base, an acylating agent, and an acylation catalyst in a solvent to afford a compound of Formula (12)



Step (h) reacting a compound of Formula (12) with HO-M in an alcohol of Formula (17) or (17b)

$\text{HOCH}_2\text{-Aryl}$ (17) or HO-Allyl (17b)

wherein M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum, or with a compound of Formula (16) or (16b)



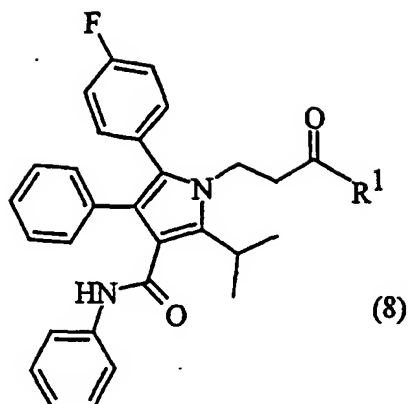
wherein M is as defined above in an alcohol of Formula (17) or (17b)

wherein aryl or allyl in a compound of Formula (16) or (16b) and (17) or (17b) is the same, in a solvent followed by the addition of hydrogen in the presence of a catalyst and an acid to afford the compound of Formula (13).

2. The process according to Claim 1, wherein the catalyst in Step (f) is $\text{RuCl}_2(\text{DMF})_n(\text{R})\text{-(+)-Cl-MeO-BIPHEP}$.

3. A process for the preparation of a compound of Formula (8)

-68-

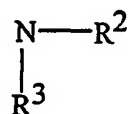


wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

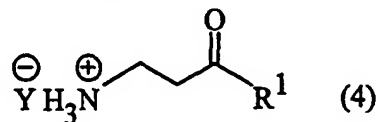
$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

-69-

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and R is alkyl, aryl, arylalkyl, or heteroaryl which comprises:

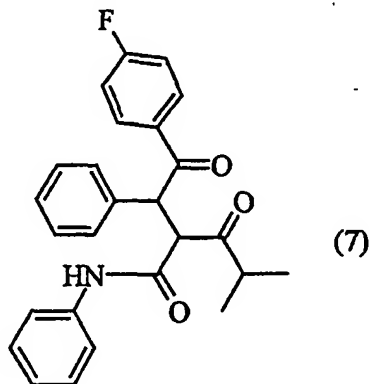
reacting a compound of Formula (4)



- 5 wherein Y is Cl, Br, TsO, MsO, or HSO_4 , and R^1 is as defined above with a compound of Formula (20)



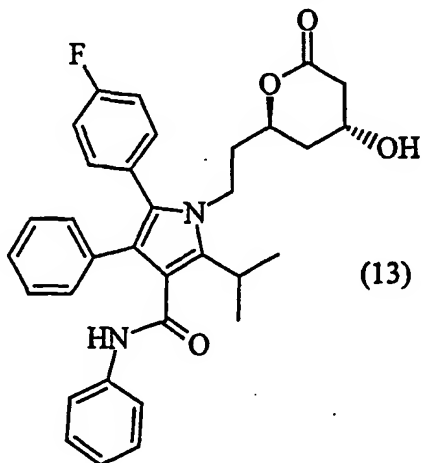
wherein R is as defined above and M is sodium, lithium, potassium, zinc, magnesium, copper, calcium, or aluminum with Compound (7)



10

in a solvent with removal of water to afford a compound of Formula (8).

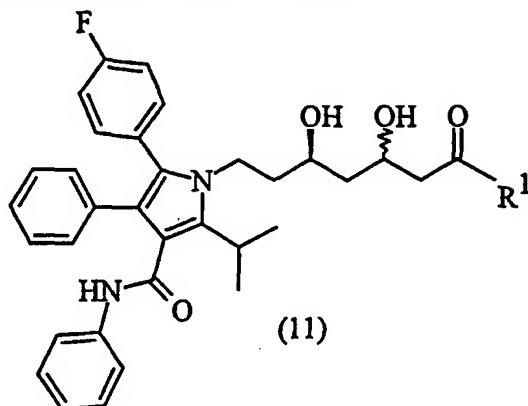
4. A process for the preparation of compound (13)



-70-

which comprises:

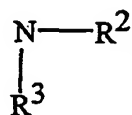
Step (a) reacting a compound of Formula (11)

wherein R^1 is -XR wherein

5

X is O,

S, or

Se, or R^1 iswherein R^2 or R^3 is independently

10

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

 R^2 and R^3 together are-(CH₂)₄-,

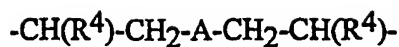
15

-(CH₂)₅-,-(CH(R⁴)-CH₂)₃-,-(CH(R⁴)-CH₂)₄-,-(CH(R⁴)-(CH₂)₂-CH(R⁴))-,-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,

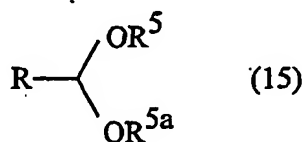
20

-CH₂-CH₂-A-CH₂-CH₂-,-CH(R⁴)-CH₂-A-CH₂CH₂-,

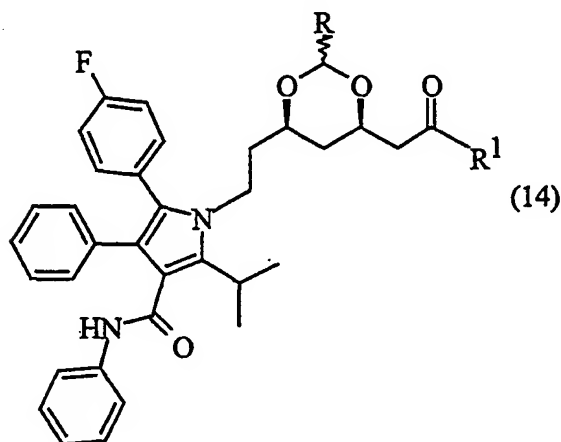
-71-



wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and R is alkyl, aryl, arylalkyl, or heteroaryl with an acetal of Formula (15)



wherein R^5 and R^{5a} are independently the same or different and are methyl, ethyl or $-(\text{CH}_2)_n-$ wherein n is an integer of 2 to 4, and R is as defined above in a solvent in the presence of an acid followed by the addition of an aldehyde corresponding to the previous acetal in the presence of a base to afford a compound of Formula (14)

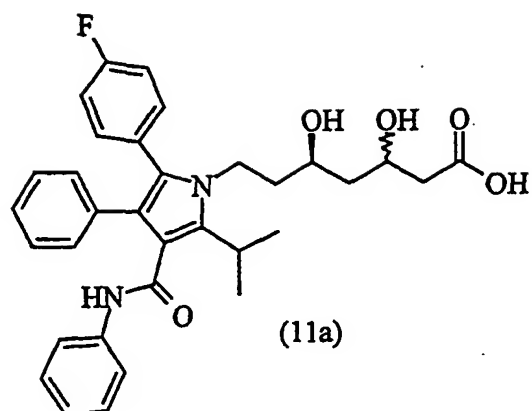


wherein R^1 and R are as defined above;

Step (b) reacting a compound of Formula (14) in a solvent in the presence of an acid or optionally reaction with hydrogen in the presence of a catalyst and an acid in a solvent to afford the compound of Formula (13); and

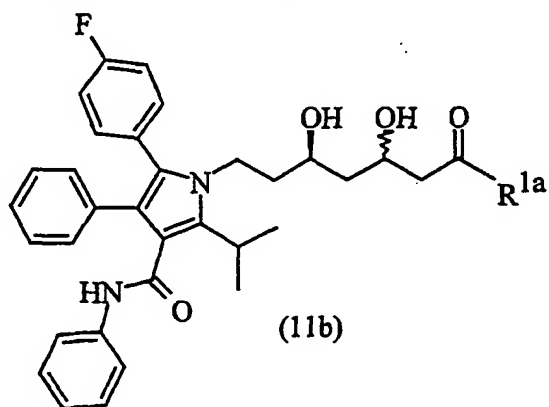
Step (c) alternatively, reacting a compound of Formula (11) or (11a) in a

-72-



solvent in the presence of an acid to afford a compound of Formula (13).

5. A process for the preparation of a compound of Formula (11b)

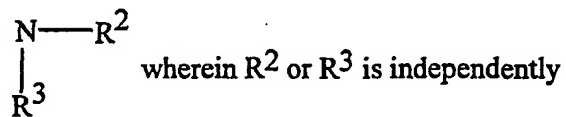


5 wherein R^{1a} is OH, -XR wherein

X is O,

S,

Se, or R^{1a} is



10

alkyl,

cycloalkyl,

arylalkyl, or

aryl, or

R^2 and R^3 together are

-73-

-(CH₂)₄-,-(CH₂)₅-,-(CH(R⁴)-CH₂)₃-,-(CH(R⁴)-CH₂)₄-,

5

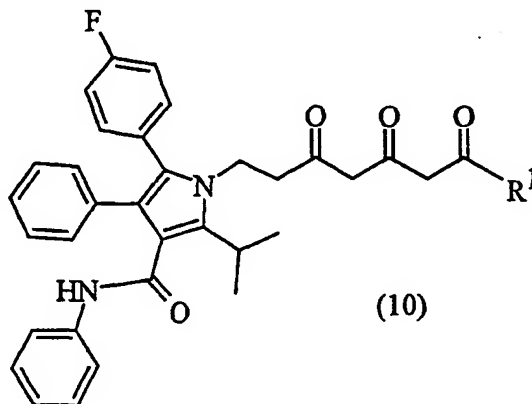
-(CH(R⁴)-(CH₂)₂-CH(R⁴))-,-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,-CH₂-CH₂-A-CH₂-CH₂-,-CH(R⁴)-CH₂-A-CH₂CH₂-,-CH(R⁴)-CH₂-A-CH₂-CH(R⁴)-

10

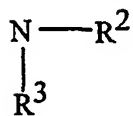
wherein R⁴ is alkyl of from one to four carbon atoms, A is O, S, or N, and

R is alkyl, aryl, arylalkyl, or heteroaryl which comprises:

Step (a) reacting a compound of Formula (10)



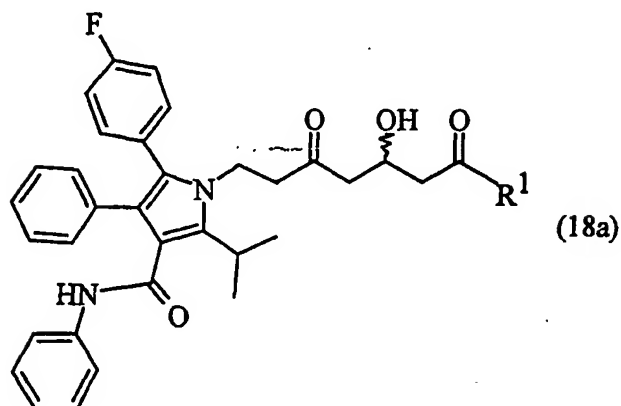
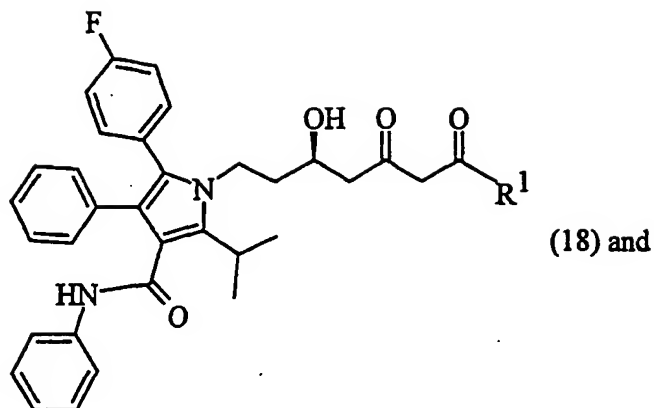
wherein R¹ is XR or R¹ is



15

wherein X, R, R², and R³ are as defined above with one mole of hydrogen in the presence of a catalyst in a solvent in the presence of an acid to afford compounds of Formula (18) and/or Formula (18a)

-74-

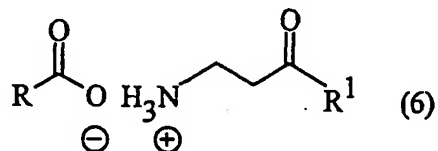


wherein R^1 is as defined above; and

Step (b) reacting either a compound of Formula (18) or (18a) with
 5 hydrogen in the presence of a catalyst in a solvent in the presence
 of an acid to afford a compound of Formula (11b).

6. The process according to Claim 5, wherein the catalyst in Step (a) or (b) is
 $RuCl_2(DMF)_n((R)-(+)-Cl-MeO-BIPHEP)$.

7. A compound of Formula (6)



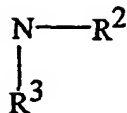
wherein R is alkyl, aryl, arylalkyl, or heteroaryl, and

wherein R^1 is -XR wherein

X is O,

-75-

S, or

Se, or R¹ iswherein R² or R³ is independently

alkyl,

cycloalkyl,

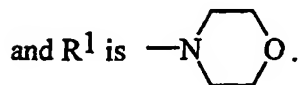
arylalkyl, or

aryl, or

R² and R³ together are-(CH₂)₄-,-(CH₂)₅-,-(CH(R⁴)-CH₂)₃-,-(CH(R⁴)-CH₂)₄-,-(CH(R⁴)-(CH₂)₂-CH(R⁴))-,-(CH(R⁴)-(CH₂)₃-CH(R⁴))-,-CH₂-CH₂-A-CH₂-CH₂-,-CH(R⁴)-CH₂-A-CH₂CH₂-,-CH(R⁴)-CH₂-A-CH₂-CH(R⁴)-wherein R⁴ is alkyl of from one to four carbon atoms, A is O, S, or N, and

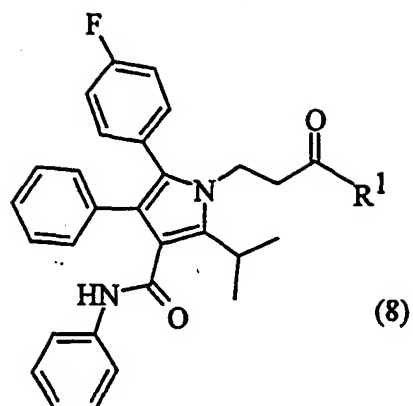
R is as defined above.

- 20 8. The compound according to Claim 7, wherein R is PhCH₂- or (CH₃)₃-C-,



9. A compound of Formula (8)

-76-

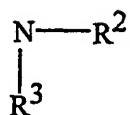


wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

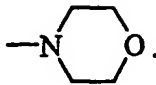
$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

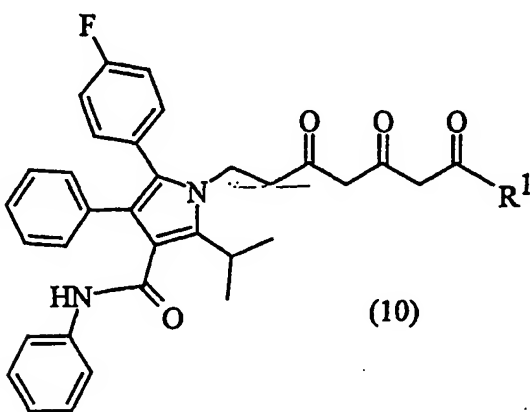
$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

-77-

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and R is alkyl, aryl, arylalkyl, or heteroaryl.

10. The compound according to Claim 9, wherein R^1 is .
11. A compound of Formula (10) or a pharmaceutically acceptable salt thereof

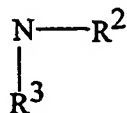


wherein R^1 -XR wherein

X is O,

S, or

Se, or R^1 is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl or

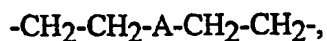
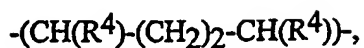
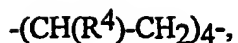
R^2 and R^3 together are

$-(CH_2)_4-$,

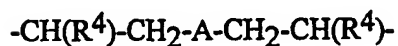
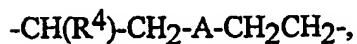
$-(CH_2)_5-$,

$-(CH(R^4)-CH_2)_3-$,

-78-



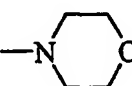
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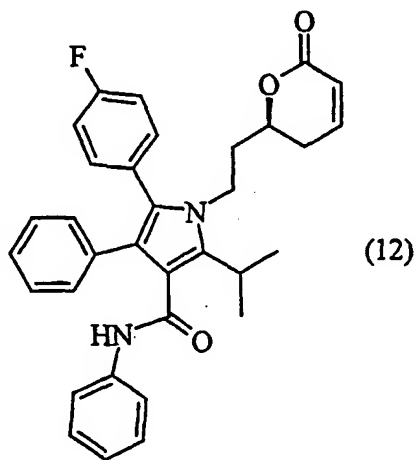
wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and
R is alkyl, aryl, arylalkyl, or heteroaryl.

12. The compound according to Claim 11, wherein R^1 is -O-tertiary butyl,

10

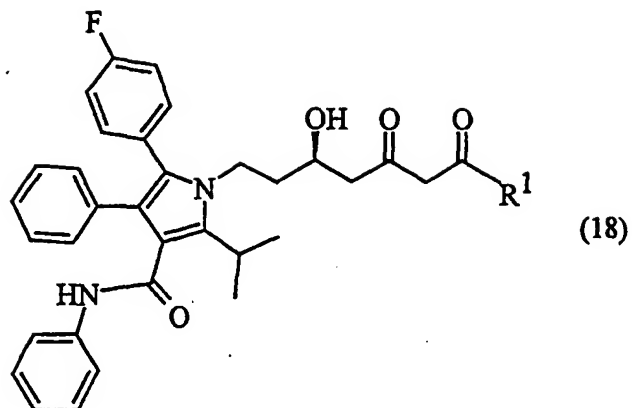
-O-isopropyl, -O-ethyl, -O-methyl, , or -NMe₂.

13. A compound of Formula (12)



14. A compound of Formula (18) or a pharmaceutically acceptable salt thereof

-79-

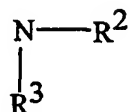


wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl or

R^2 and R^3 together are

$-(\text{CH}_2)_4-$,

$-(\text{CH}_2)_5-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_3-$,

$-(\text{CH}(\text{R}^4)-\text{CH}_2)_4-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_2-\text{CH}(\text{R}^4))-$,

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

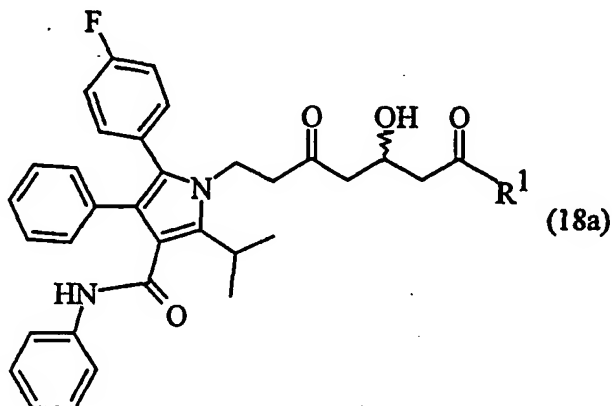
$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

-80-

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and
R is alkyl, aryl, arylalkyl, or heteroaryl.

15. A compound of Formula (18a) or a pharmaceutically acceptable salt thereof

5



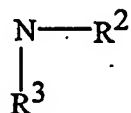
wherein R^1 is -XR wherein

X is O,

S, or

Se, or R^1 is

10



wherein R^2 or R^3 is independently

alkyl,

cycloalkyl,

arylalkyl, or

aryl or

15

R^2 and R^3 together are

$-(CH_2)_4-$,

$-(CH_2)_5-$,

$-(CH(R^4)-CH_2)_3-$,

$-(CH(R^4)-CH_2)_4-$,

20

$-(CH(R^4)-(CH_2)_2-CH(R^4))-$,

-81-

$-(\text{CH}(\text{R}^4)-(\text{CH}_2)_3-\text{CH}(\text{R}^4))-$,

$-\text{CH}_2-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2\text{CH}_2-$,

$-\text{CH}(\text{R}^4)-\text{CH}_2-\text{A}-\text{CH}_2-\text{CH}(\text{R}^4)-$

5

wherein R^4 is alkyl of from one to four carbon atoms, A is O, S, or N, and
R is alkyl, aryl, arylalkyl, or heteroaryl.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 July 2002 (18.07.2002)

PCT

(10) International Publication Number
WO 02/055519 A3

- (51) International Patent Classification⁷: **C07D 405/06**, 207/34, 295/18
- (21) International Application Number: **PCT/IB01/02729**
- (22) International Filing Date:
27 December 2001 (27.12.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/260,505 9 January 2001 (09.01.2001) US
- (71) Applicant (*for all designated States except US*):
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- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BUTLER, Donald, Eugene** [US/US]; Pfizer Global Research & Development, Ann Arbor Laboratories, 2800, Plymouth Road, Ann Arbor, MI (US). **DEJONG, Randall, Lee** [US/US]; Pfizer Global Research & Development, Ann Arbor Laboratories, 2800, Plymouth Road, Ann Arbor, MI (US). **NELSON, Jade, Douglas** [US/US]; Pfizer Global Research & Development, Ann Arbor Laboratories, 2800, Plymouth Road, Ann Arbor, MI (US). **PAMMENT, Michael, Gerard** [US/US]; Pfizer Global Research & Development, Ann Arbor Laboratories, 2800, Plymouth Road, Ann Arbor, MI (US). **STUK, Timothy, Lee** [US/US]; Pfizer Global Research & Development, Ann Arbor Laboratories, 2800, Plymouth Road, Ann Arbor, MI (US).
- (74) Agents: **LUMB, J.; Trevor et al.**; c/o Simpson, Alison, Urquhart-Dykes & Lord, 30 Welbeck Street, London, W1G 8ER (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:
19 September 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: NOVEL PROCESS FOR THE SYNTHESIS OF 5-(4-FLUOROPHENYL)-1-[2-((2R, 4R)-4-HYDROXY-6-OXO-TETRAHYDRO-PYRAN-2-YL)-ETHYL]-2-ISOPROPYL-4-PHENYL-1H-PYRROLE-3-CARBOXYLIC ACID PHENYLAMIDE

(57) Abstract: An improved process for the preparation of 5-(4-fluorophenyl)-1-[2-((2R,4R)-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethyl]-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid phenylamide by a novel synthesis is described where methyl cyanoacetate is converted in eight operations or fewer to the desired product, as well as other valuable intermediates used in the process.

WO 02/055519 A3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/02729

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06 C07D207/34 C07D295/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 247 633 A (WARNER LAMBERT CO) 2 December 1987 (1987-12-02) page 5 -page 7; claims & US 4 681 893 A 21 July 1987 (1987-07-21) cited in the application ---	1-15
A	EP 1 061 073 A (WARNER LAMBERT CO) 20 December 2000 (2000-12-20) page 5 -page 7; claims ---	1-15
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☒ Patent family members are listed in annex.

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8 document member of the same patent family

Date of the actual completion of the international search

5 July 2002

Date of mailing of the international search report.

15/07/2002

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Chouly, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/02729

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ROTH B D ET AL: "INHIBITORS OF CHOLESTEROL BIOSYNTHESIS. 3. TETRAHYDRO-4-HYDROXY-6-(2-(1H-PYRROL-1-YL)ETHYL)-2H-PYRAN-2-ONE INHIBITORS OF HMG-COA REDUCTASE. 2. EFFECTS OF INTRODUCING SUBSTITUENTS AT POSITIONS THREE AND FOUR OF THE PYRROLE NUCLEUS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 1, January 1991 (1991-01), pages 357-366, XP002922115 ISSN: 0022-2623 the whole document</p>	1-15
A	<p>BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 the whole document</p>	1-15

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